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Methylarsenic compounds

MAK Value Documentation – Translation of the German version from 2014

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Keywords: methylarsenic compounds; bladder; kidney; carcinogenicity; genotoxicity; germ cell mutagenicity; skin absorption; developmental toxicity; sensitization

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Methylarsenic compounds

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated methylarsenic compounds considering all toxicological endpoints. Available publications and unpublished study reports are described in detail.
Methylarsenic compounds are the carcinogenic metabolites of arsenic and its inorganic compounds, which are proven human carcinogens. Methylated arsenic compounds are able to interfere with all important cellular processes. In mice and rats, dimethylarsinic acid was clearly carcinogenic. Trimethylarsine oxide caused liver adenomas in F344 rats and with methylarsenic acid, preneoplastic liver effects were found. If all aspects are considered, methylarsenic compounds are classified in Carcinogen Category 1. Methylarsenic compounds are genotoxic in vitro and in vivo. As they are bioavailable and can reach the germ cells, they are classified in Category 3 A for Germ Cell Mutagens. Methylarsenic compounds are genotoxic carcinogens, for which no safe systemic exposure can be estimated. It must be assumed that even small amounts absorbed percutaneously increase the carcinogenic risk. Therefore, methylarsenic compounds are designated with an "H" (for substances that can be absorbed through the skin in toxicologically relevant amounts). Dimethylarsinic acid induced developmental toxicity in rats. Apart from a well-documented case report, there are no clear findings available to conclude a skin-sensitizing potential in humans.

Keywords

monomethylarsenic compounds; methylarsonous acid; methylarsonic acid; methylarsine diiodide; diiodomethylarsine; sodium methylarsonate; disodium methylarsonate; methylthioarsonic acid; dimethylarsenic compounds; dimethylarsinous acid; dimethylarsinic acid; cacodylic acid; iododimethylarsine; sodium dimethylarsinate; dimethylthioarsinic acid; dimethyldithioarsinic acid; trimethylarsenic compounds; trimethylarsine; trimethylarsine oxide; trimethylarsine sulfide; tetramethylarsenic compounds; tetramethylarsonium iodide; mechanism of action; (sub) acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; reproductive toxicity; fertility; developmental toxicity; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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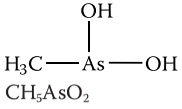
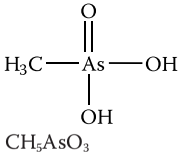
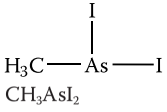
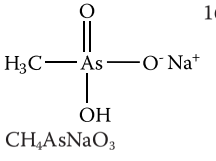
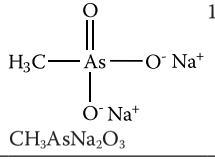
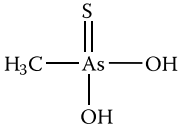
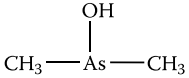
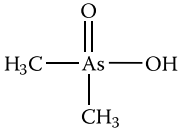
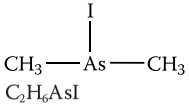
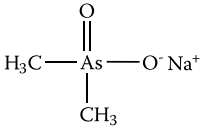
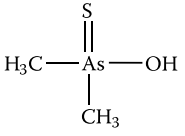
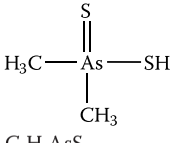
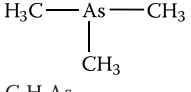
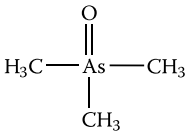
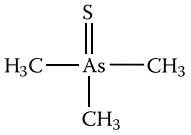
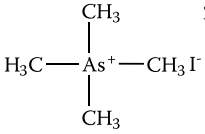
Methylarsenic compounds

MAK value	**–**
Peak limitation	**–**
Absorption through the skin (2013)	**H**
Sensitization	**–**
Carcinogenicity (2013)	**Category 1**
Prenatal toxicity	**–**
Germ cell mutagenicity (2013)	**Category 3A**
BAT value	**–**

Compound	Molecular formula	Molecular weight [g/mol]	CAS No.	Melting point	Vapour pressure	log K_{OW}[1)]	Solubility
Monomethylarsenic compounds							
Methylarsonous acid	 CH_5AsO_2	123.97	25400-23-1				
Methylarsonic acid	 CH_5AsO_3	139.97	124-58-3	160.5 °C [a)]	2.16×10^{-3} hPa at 25 °C (cal.) [a)]	−1.18 (cal.) [a)]	2.56×10^{5} mg/l at 20 °C [a)]
Methylarsine diiodide, Diiodomethylarsine	 CH_3AsI_2	343.76	7207-97-8				
Sodium methyl-arsonate	 CH_4AsNaO_3	161.95	2163-80-6	130–140 °C [g)] 113–116 °C [h)]	0.1×10^{-6} hPa at 25 °C [b)]	−3.1 [b)]	5.8×10^{5} mg/l at 20 °C [b)]
Disodium methylarsonate	 $CH_3AsNa_2O_3$	183.93	144-21-8	132–139 °C [c)]	1.33×10^{-7} hPa at 25 °C [c)]	−5.34 (cal.) [c)]	4.32×10^{5} mg/l at 25 °C [c)]

Compound	Molecular formula	Molecular weight [g/mol]	CAS No.	Melting point	Vapour pressure	log K_{OW}[1)]	Solubility
Methylthioarsonic acid	 CH_5AsO_2S	156.00	937022-98-5				
Dimethylarsenic compounds							
Dimethylarsinous acid	 C_2H_7AsO	122.00	55094-22-9				
Dimethylarsinic acid, Cacodylic acid	 $C_2H_7AsO_2$	138.00	75-60-5	195 °C [d)]	1.33×10^{-7} hPa (cal.) [d)]	0.36 (cal.) [d)]	2.0×10^6 mg/l at 25 °C [d)]
Iododimethylarsine	 C_2H_6AsI	231.89	676-75-5				

Compound	Molecular formula	Molecular weight [g/mol]	CAS No.	Melting point	Vapour pressure	log K_{OW}[1)]	Solubility
Sodium dimethylarsinate	 $C_2H_6AsNaO_2$	159.98	124-65-2	200 °C [e)]	3.9×10^{-8} hPa at 25 °C (cal.) [e)]	−2.18 (cal.) [e)]	2.0×10^6 mg/l at 25 °C [e)]
Dimethylthioarsinic acid	 C_2H_7AsOS	154.06	754217-65-7				
Dimethyldithioarsinic acid	 $C_2H_7AsS_2$	170.13	65165-11-9				
Trimethylarsenic compounds							
Trimethylarsine	 C_3H_9As	120.02	593-88-4	−87.3 °C [f)]	361.3 hPa at 25 °C (cal.) [f)]	2.32 (cal.) [f)]	1470 mg/l at 25 °C (cal.) [f)]

Compound	Molecular formula	Molecular weight [g/mol]	CAS No.	Melting point	Vapour pressure	log K_{OW}[1)]	Solubility
Trimethylarsine oxide	 C_3H_9AsO	136.02	4964-14-1				
Trimethylarsine sulfide	 C_3H_9AsS	152.09	26386-93-6				
Tetramethylarsenic compounds							
Tetramethyl-arsoniumiodide	 $C_4H_{12}AsI$	261.96	5814-20-0				

[a–f)] SRC (2013 a–f),
[g)] ATSDR (2007),
[h)] Chemical Book (2013); cal.: calculated
[1)] octanol/water partition coefficient

This documentation is based on reviews of the toxicological profile of methylarsenic compounds, for example documentation from the Agency for Toxic Substances and Disease Registry (ATSDR 2007) and a report by the International Agency for Research on Cancer (IARC 2012).

Methylarsonic acid and dimethylarsinic acid and their salts were widely used as pesticides and herbicides. Nowadays, most of these applications are diminishing or prohibited in Europe.

In 2009, the US Environmental Protection Agency (US EPA) published a product cancellation order whereby the application of organic arsenic pesticides was to be discontinued by 2013 at the latest. However, the herbicide sodium methylarsonate used against broad-leafed weeds is exempt from this regulation, and will continue to be authorized for use in the case of cotton. Disodium methylarsonate, which has commonly been applied to cotton fields in small quantities, has, however, become prohibited (US EPA 2009).

Methylarsonous acid ($CH_3As(OH)_2$) is produced for example in the form of an aqueous solution from methyloxoarsine (CH_3AsO) or diiodomethylarsine (CH_3AsI_2), and dimethylarsinous acid ($(CH_3)_2AsOH$) from iododimethylarsine ($(CH_3)_2AsI$) (Schwerdtle et al. 2003 a).

In humans and animals, methylated organic arsenic compounds are formed during the metabolism of inorganic arsenic compounds (see Section 3.2).

1 Toxic Effects and Mode of Action

Methylarsenic compounds can be absorbed by inhalation, ingestion, or through the skin. After oral administration of methylarsonic acid or dimethylarsinic acid, in rats and mice more than 80% of the dose is absorbed, subsequently distributed to the bladder, kidneys, lungs, liver, spleen, intestine and testes and then rapidly eliminated, above all with the urine. In rats, accumulation in the erythrocytes has been demonstrated.

Methylarsenic compounds are converted by methylation into higher dimethylarsenic or trimethylarsenic compounds or even thiomethylarsenic compounds. More than 80% of the methylarsonous acid is methylated to form dimethylarsinic acid, about 10% of the methylarsonic acid to dimethylarsinic acid, about 40% of dimethylarsinic acid to trimethylarsine oxide and about 2% of the trimethylarsine oxide to the tetramethylarsonium ion.

In humans, single exposures to methylarsenic compounds can cause nausea, stomach cramps, headaches, dizziness, paralysis, irregular breathing and unconsciousness. Irritation of the skin and eyes and also itchy skin eruptions have been described.

In experiments with animals, the symptoms of acute intoxication are restricted motility, laboured breathing, and haemorrhages in the stomach, intestine, caecum, lungs and kidneys.

After oral administration for 8 weeks, dimethylarsinic acid doses of about 1.5 mg/kg body weight and day and above produced dose-dependent proliferation of the cells of the urothelium of the bladder in rats, and doses of 3.5 mg/kg body weight and day and above led to a significantly increased incidence of alveolar and

papillary adenomas in mice after 50 weeks. In various initiation–promotion studies with rats and mice, methylated arsenic compounds caused preneoplastic changes or tumours in the bladder, liver, kidneys or lungs. Methylarsenic compounds are tumour promotors.

In rats, carcinogenic effects were observed in the bladder after dietary administration of dimethylarsinic acid doses of about 2.5 mg/kg body weight and day (males) and about 5 mg/kg body weight and day (females). Trimethylarsine oxide administered with the drinking water caused a significant increase in liver adenomas in male rats after two years. After treatment with methylarsonic acid, preneoplastic lesions such as hyperplasia were found in the liver at 2 mg/kg body weight and day and above and glutathione S-transferase placental form positive foci were demonstrated at 8 mg/kg body weight and day.

Methylarsenic compounds are not mutagenic in bacteria. In mammalian cells, they cause oxidative DNA damage, inhibition of DNA repair, chromatid and chromosome damage, and aneuploidy. In F344 rats, oxidative DNA damage in the liver has been demonstrated, and in CD1 mice, DNA strand breaks in the lungs and aneuploidy in the bone marrow occur. In Muta™ mice, point mutations are found in peripheral reticulocytes, the lungs, liver, bladder and bone marrow, and also micronuclei in peripheral reticulocytes.

After mating with male mice treated with sodium methylarsonate (12 mg/kg body weight and day), some of the untreated females were without offspring. Pre-implantation losses occurred in rats at dimethylarsinic acid doses of 12 mg/kg body weight and day, and post-implantation losses, skeletal variations and delayed ossification in the development of the sternum, skull and tail bones at 36 mg/kg body weight and day and above.

2 Mechanism of Action

2.1 Effects on cellular macromolecules

Oxidative damage

A major cause of arsenic toxicity is the impairment of cellular redox homoeostasis as a result of the induction of oxidative stress and the interaction of arsenic with specific proteins responsible for the maintenance of genomic stability and cellular redox regulation (Hartwig 2013).

Oxidative stress is caused by the increased formation of reactive oxygen or nitrogen compounds and leads to damage to proteins, lipids and DNA. Free radicals such as dimethylarsenic peroxyl radicals, superoxide anion radicals or hydroxyl radicals, or also peroxinitrite, are held responsible for the effects of methylated arsenic compounds (Dopp et al. 2010 b; Eblin et al. 2006; Hartwig and Schwerdtle 2009; Kinoshita et al. 2007 a, b; Schwerdtle et al. 2003 a; Shi et al. 2004; Tennant and Kligerman 2011; Yamanaka et al. 2003, 2009).

Arsenic compounds impair the redox homoeostasis by reducing the intracellular glutathione concentration (Kitchin 2001; Leffers et al. 2013 a). This can take place by the formation of a complex with the thiol group of glutathione and subsequent deg-

radation of the glutathione, as a consequence of glutathione consumption during arsenic metabolism or by affecting glutathione-dependent enzymes (Chouchane and Snow 2001; Styblo et al. 1997).

In rat liver cells (RLC-16) the formation of reactive oxygen species took place in different organelles depending on the methylarsenic compound used. The target organelles for methylarsonous acid are the mitochondria. As a result of the inhibition of complex II and complex IV of the respiratory chain, increasing amounts of reactive oxygen species are formed (Naranmandura et al. 2011 a). By comparison, dimethylarsinous acid stimulates the formation of reactive oxygen species in the endoplasmic reticulum (ER) by increasing phosphorylation of the protein-kinase-like ER-kinase (Naranmandura et al. 2012).

Interaction with thiol groups

Another fundamental mechanism of the toxicity of arsenic is its interaction with thiols. Because of their high affinity, methylated arsenic compounds are able to bind readily to thiol groups, thereby oxidizing or complexing them. Generally, trivalent arsenic compounds such as methylarsonous acid demonstrate a greater affinity to dithiols or trithiols than to monothiols (Beyersmann and Hartwig 2008; Kitchin and Wallace 2008; Shi et al. 2004). In proteins, this oxidation can produce conformation changes and loss of function (Naranmandura et al. 2012).

Depending on the initial compound, potentially toxic intermediates such as oxygen or sulfur radicals can be formed at the intracellular level, for example by the direct transfer of electrons of non-protein-thiols, such as glutathione and cysteine (Yao et al.2008).

Changes to zinc-binding proteins

Zinc-binding structures, including so-called "zinc fingers", are one of the factors responsible for interactions with DNA and RNA or for protein/protein interactions and are found in replication, transcription and translation factors, DNA repair proteins or also in proteins participating in metabolism and in the regulation of the cell cycle and apoptosis (Laity et al. 2001; Krishna et al. 2003; Piatek et al. 2008). Their common structural element is a zinc ion, which is complexed by invariant cysteine or histidine residues and ensures correct protein folding. Owing to its high affinity to thiols, the zinc finger structure constitutes a molecular site of attack for the organic arsenic compounds methylarsonous acid and dimethylarsinous acid. In the zinc finger peptide of XPA (XPAzf), a component of the nucleotide excision repair complex, in which zinc is complexed via four cysteine residues, methylarsonous acid produced a complex while releasing the zinc ion, which contained either two molecules or only one molecule of methylarsonous acid (Piatek et al. 2008). In addition, the tumour suppressor protein p53, which binds zinc with three cysteines and one histidine (Levine 1997), can be impaired by methylated trivalent arsenic compounds and consequently can no longer exert its important function as regulator of the cell cycle or inducer of apoptosis (Shen et al. 2008).

Also the reactive oxygen and nitrogen species generated by the organic arsenic compounds can, via oxidation of the thiol groups of the zinc finger, result in the formation of disulfide bridges, and thus to a loss of function of the protein.

2.2 Effects on cellular regulation mechanisms

Methylated arsenic compounds affect the signal transduction of cells (Beyersmann and Hartwig 2008; Eblin et al. 2007; Kumagai and Sumi 2007), for example via the induced reactive oxygen and nitrogen compounds, which are able to interfere with signal transduction chains as secondary messengers (Brigelius-Flohé and Flohé 2011; D'Autreaux and Toledano 2007; Giles 2006; Ray et al. 2012). In addition, there are some redox-regulated signal pathways which are controlled by the reversible oxidation and reduction of the thiol groups. The intracellular redox status therefore appears to be decisive for the correct functioning of many enzymes, and changes in redox status act as a signal transduction mechanism (Hartwig 2013).

The reactive species induced by methylated arsenic compounds are able to change various signal cascades and to interfere in cellular signal transduction via mitogen-activated protein kinases (MAPK), p38, c-Jun N-terminal kinase 3 (JNK3) (Namgung and Xia 2001) and transcription factor AP-1 or NFκB (Leonard et al. 2004).

Cellular signal transduction can also be disturbed by effects on calcium homoeostasis. Ca^{2+} ions are the major messenger substances of various signal transduction cascades. Arsenic compounds induce an increase in the cytosolic Ca^{2+} concentration. The increased release of Ca^{2+} ions, for example from HeLa-S3 cells, was found for various methylated arsenic compounds, such as methylarsonic acid, dimethylarsinic acid and trimethylarsine oxide. It was not clarified whether this Ca^{2+} release was an energy-consuming process, or occurred as a result of changes in other ion transporters (Florea et al. 2005). Even slight changes in the intracellular Ca^{2+} concentration can cause changes in cell proliferation or cell differentiation or lead to the modulation of apoptosis (Orrenius et al. 2003). By impairing Ca^{2+} homoeostasis, methylated arsenic compounds are also able to interfere with other important processes, such as transmitter and hormone release, DNA repair, gene expression and DNA replication.

2.3 Genotoxicity

Oxidative damage to DNA

Oxidative DNA damage is induced by free radicals produced from the reactions of methylated arsenic compounds with molecular oxygen (dimethylarsenic peroxyl radical or superoxide anion radical) (Eblin et al. 2006; Nesnow et al. 2002; Schwerdtle et al. 2003 a; Yamanaka and Okada 1994; Yamanaka et al. 1989, 1991, 2001), iron (Ahmad et al. 1999, 2000, 2002) or nitrogen (Bau et al. 2001; Wang et al. 2007) or by modulation of the NO synthases (Kumagai and Pi 2004; Kumagai and Sumi 2007; Li et al. 2007).

The main reactive oxygen compounds participating in DNA damage are hydroxyl radicals, singlet oxygen ($^1O_2$) and single-electron oxidants. The hydroxyl radical is capable of producing single strand breaks as the result of hydrogen abstraction from 2-deoxyribose residues (Aydogan et al. 2002; Chan et al. 2010; Dedon 2008; Hartwig 2013; Pogozelski and Tullius 1998). Singlet oxygen reacts particularly with guanine with the formation of 8-oxo-7,8-dihydroguanine (8-oxoguanine), without

thereby inducing the formation of further reaction products (Cadet et al. 2008). If the oxidized DNA bases induced by methylated arsenic compounds, for example 8-oxoguanine (Schwerdtle et al. 2003 a), are not repaired, G:C→T:A transversions can occur (Moriya 1993).

Indirect genotoxic effects

The interaction of organic arsenic compounds with different proteins or genes essential for the repair of damaged DNA is one of the factors responsible for indirect genotoxic effects.

Examples for the inhibition of DNA repair proteins are found in the effects of methylated arsenic compounds on the human xeroderma pigmentosum protein A (XPA) involved in nucleotide excision repair (NER) or on the formamidopyrimidine DNA glycosylase (Fpg) participating in base excision repair (BER) and originating from Escherichia coli (Schwerdtle et al. 2003 a, b) or 8-oxoguanine DNA glycosylase (Ebert et al. 2011) and on poly(ADP-ribosyl)ation (Ebert et al. 2013), which is catalysed mainly by the zinc finger protein PARP-1 (Hartwig et al. 2003 a, b; Walter et al. 2007).

Changes in DNA methylation characterize nearly all tumour types and are accompanied by changes in histone acetylation and the expression of the associated genes (Jones et al. 1998; Neuhausen et al. 2006; Salem et al. 2000). Organic arsenic compounds can produce modifications in histone acetylation and change DNA methylation. This was demonstrated after treatment with methylarsonous acid in human urothelial cells in the histone H3 and as a result of DNA hypermethylation in hypoacetylated promoters (Jensen et al. 2008) as well as after the administration of methylarsonic acid or dimethylarsinic acid in homozygous Tg.AC mice (Xie et al. 2004). Changes in the DNA methylation pattern are explained by a changed S-adenosyl methionine pool or the down regulation of DNA methyltransferases (IARC 2012).

As a result of an increase in the formation of so-called "micro-RNA", a class of RNA not coding proteins, methylated arsenic compounds can inhibit the expression of regulator genes via binding to the corresponding mRNA and their subsequent degradation (Ren et al. 2011).

Among the indirect genotoxic effects are also changes in the expression of genes of specific DNA repair proteins. Methylated arsenic compounds thus cause a reduction in xeroderma pigmentosum protein C (XPC) expression, which is a major damage recognition protein in nucleotide excision repair (Nollen et al. 2008).

2.4 Carcinogenicity

The mechanisms described above are held responsible for the carcinogenicity of methylarsenic compounds; these include the induction of oxidative stress, the impairment of DNA repair processes, changes in DNA methylation patterns, the modulation of gene expression, increased cell proliferation, the inhibition of p53 and interactions with cellular redox regulation. An important role is attributed to the epigenetic mechanisms such as changes in DNA methylation, histone modification and microRNA expression.

2.5 Effect size of various organic arsenic compounds

In most studies, the toxicity of methylarsonous acid and dimethylarsinous acid was greater than that of inorganic arsenite or methylarsonic acid or dimethylarsinic acid, as has been found in studies of cytotoxicity in Chang hepatocytes (ATCC CCL-13) (Petrick et al. 2000; Styblo et al. 2000), or that of the formation of radicals in human urothelial cells and primary human hepatocytes (Dopp et al. 2008), or of DNA damage in plasmids (Andrewes et al. 2003) or HeLa-S3 cells (Schwerdtle et al. 2003 a) or that of the clastogenic effects in human lymphocytes (Kligerman et al. 2003), or the induction of apoptosis in leukaemia cells (Chen et al. 2003) or the proliferation of keratinocytes (Mudipalli et al. 2005).

The explanation for the higher toxicity of methylarsonous acid and dimethylarsinous acid compared with that of methylarsonic acid and dimethylarsinic acid, for example in the inhibition of glutathione reductase (Chouchane and Snow 2001) or thioredoxin reductase (Lin et al. 1999) or in proteins and peptides, such as the bacterial formamidopyrimidine-DNA glycosylase (Fpg) (Schwerdtle et al. 2003 a), XPAzf (Schwerdtle et al. 2003 b) or poly(ADP-Ribose)polymerase-1 (PARP-1) (Walter et al. 2007), could be that the first-mentioned compounds are present mainly in uncharged form, whereas the latter two compounds are charged and can therefore be absorbed less easily by cells (Styblo et al. 1999). Methylarsonous acid and dimethylarsinous acid are able to pass the cell membranes of the urinary epithelium, Chinese hamster ovary and liver more effectively than methylarsonic acid and dimethylarsinic acid (Dopp et al. 2005, 2010 a, b). In addition, methylarsonous acid and dimethylarsinous acid are able to release the zinc ions from zinc finger proteins more effectively and at very much lower concentrations (Piatek et al. 2008; Schwerdtle et al. 2003 b), thus resulting in major functional disorders.

Organic thioarsenic compounds are considerably more toxic than methylarsonic acid and dimethylarsinic acid (Bartel et al. 2011; Suzuki et al. 2010) or similar in effect (Naranmandura et al. 2009; Ochi et al. 2008) or more effective than dimethylarsinous acid (Naranmandura et al. 2011 b) as, due to their high bioavailability (Leffers et al. 2013 a, b; Naranmandura et al. 2007 a), they are very well absorbed at the intracellular level and then reduced mainly to dimethylarsinous acid (Naranmandura et al. 2012).

The lower toxicity of methylarsonic acid in the whole organism could also be attributed, with the exception of the cellular mechanisms, to more rapid elimination (Hughes et al. 2005).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

3.1.1 Absorption

Inhalation

In view of the systemic effects in animal studies, methylarsenic compounds can be assumed to be absorbed by inhalation (see Section 5.2.1).

Oral administration

Organic arsenic compounds are absorbed by humans particularly through the consumption of sea fish, crustaceans and shellfish or the seaweed used in sushi dishes (WHO 2001). Here, arsenobetaine and arsenocholine make up the greatest portion, followed by **dimethylarsinic acid**, **trimethylarsine** and **trimethylarsine oxide** (UBA 2003, 2004).

Monomethylarsenic compounds

In B6C3F1 mice the bioavailability of **methylarsonic acid** was found to be dose-dependent: 81% was absorbed after oral administration of 0.4 mg methylarsonic acid/kg body weight, compared with 60% after 4 mg methylarsonic acid/kg body weight (Hughes et al. 2005).

Dimethylarsenic compounds

More than 80% of the **dimethylarsinic acid** orally administered to rats and mice was absorbed by the gastrointestinal tract (Vahter et al.1984).

In rats, after intratracheal instillation, 92% of the administered **dimethylarsinic acid** dose was absorbed with a half-time of 2.2 minutes. After gavage administration, the amount absorbed was 66% with a half-time of 248 minutes (Stevens et al. 1977).

The uptake of orally administered ^{14}C-labelled **dimethylarsinic acid** was dose-dependent in mice, as was found in the blood, lungs, liver, kidneys, bladder and urine after doses of 0.6 or 60 mg arsenic/kg body weight after 12, 30 or 60 minutes and also after 2, 4, 8, 12 or 24 hours (Hughes et al. 2008).

Dermal absorption

Monomethylarsenic compounds

On the basis of a saturated aqueous **methylarsonic acid** solution, dermal fluxes of 87, 9.0 and 21 µg/cm^2 and hour, respectively, can be calculated using the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995). After the exposure of both hands and forearms (about 2000 cm^2) for one hour, this would correspond to the absorption of 175, 19 and 42 mg methylarsonic acid, respectively.

Dimethylarsenic compounds

Using a Franz diffusion cell, an absorption rate of 0.054 µg arsenic/cm^2 and hour (0.099 µg dimethylarsinic acid/cm^2 and hour) was obtained with **dimethylarsinic acid** in a concentration of 10 mg arsenic/l water (18.4 mg dimethylarsinic acid/l, exposure for 24 hours) applied to whole skin from a female donor. Compared with that of inorganic arsenate, the rate of dermal absorption was 59 times more rapid (Ouypornkochagorn and Feldmann 2010).

In in vitro studies with the skin of mice (0.64 cm^2), in flow-through cells containing **dimethylarsinic acid** (10 µg) dissolved in 20, 100 or 250 µl water, 4.77%, 3.09% and 0.37% of the dose was recovered in the receptor fluid after exposure for 2 hours. The pH level had no effect on absorption (Hughes et al. 1995). With the data from the most concentrated solution (10 µg/20 µl = 500 mg/l), a flux of 0.37 µg/cm^2 and

hour can be calculated. For the most diluted solution (40 mg/l), the flux is 0.029 µg/cm² and hour.

The sodium salts **sodium methylarsonate** and **disodium methylarsonate** were investigated in a similar way. Using 10 µg sodium methylarsonate in 20, 100 and 250 µl water, 0.51%, 0.86% and 0.79% of the dose was recovered in the receptor phase per hour. For disodium methylarsonate, the values were 0.76%, 0.83% and 0.76% per hour (Rahman and Hughes 1994). The highest percentage absorbed corresponds to a flux of 0.13 µg/cm² and hour for sodium methylarsonate and disodium methylarsonate.

Taking the maximum concentration for these models of 1000 g/l of an aqueous **dimethylarsinic acid** solution, dermal fluxes of 2870, 470 and 635 µg/cm² and hour are obtained with the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995), respectively. After the exposure of both hands and forearms (about 2000 cm²) to the substance for one hour this would correspond to the total absorption of 5694, 940 and 1271 mg dimethylarsinic acid, respectively. The flux calculated with the model of Fiserova-Bergerova for the concentration used in the study by Ouypornkochagorn and Feldmann (2010) agrees with the results obtained experimentally in this study.

3.1.2 Distribution

Monomethylarsenic compounds

In mice, **methylarsonic acid** is distributed rapidly throughout the body after single oral doses. The highest concentrations in tissue were found in the bladder, kidneys and lungs between 0.25 and 4 hours after the exposure. They were higher than the concentration in the blood (Hughes et al. 2005). Six hours after the ingestion of **methylarsonic acid** doses of 50 mg/kg body weight in hamsters, the highest concentrations were found in the kidneys, followed by the spleen, blood and lungs (Yamauchi et al. 1988).

After the administration of **methylarsonous acid** for 26 weeks in concentrations of 50 or 150 mg/l drinking water (doses of about 6.25 or 18.75 mg methylarsonous acid/kg body weight and day), the concentrations of methylarsonous acid and dimethylarsinic acid were determined in various organs in transgenic K6/OCD mice. As the valences of methylarsonous acid and methylarsonic acid cannot be recorded with the analytical method used, probably the concentrations of methylarsonic acid were determined here. In the bladder therefore, values of 0.09 and 0.53 µg methylarsonic acid/g tissue and 9.21 and 25.0 µg dimethylarsinic acid/g tissue were obtained for the two doses administered, respectively. In the kidneys these values were 0.43 and 1.67 µg methylarsonic acid/g tissue and 3.77 and 6.47 µg dimethylarsinic acid/g tissue, in the liver 0.08 and 0.62 µg methylarsonic acid/g tissue and 3.49 and 6.67 µg dimethylarsinic acid/g tissue, and in the lungs 0.40 and 1.38 µg methylarsonic acid/g tissue and 8.16 and 12.44 µg dimethylarsinic acid/g tissue, respectively. When a low methionine diet was administered instead of the normal diet, the concentrations of methylarsonic acid and of dimethylarsinic acid were significantly reduced in the corresponding organs (Chen et al. 2008).

In sheep and goats, after the ingestion of **sodium methylarsonate** the highest concentrations were determined after 5 hours in the blood. In the milk, only very small arsenic quantities were detectable. For elimination from the blood, half-times of 23 and 17 hours, respectively, were obtained (Shariatpanahi and Anderson 1984).

Dimethylarsenic compounds

In mice, six hours after intravenous injection of ^{74}As-**dimethylarsinic acid**, the highest radioactivity was found in the lungs > kidneys > large intestine > testes > small intestine and in the thymus and thyroid gland. The radioactivity was detectable for the longest in the lungs, intestinal wall, thyroid gland and the lenses of the eyes (Vahter et al.1984).

After intravenous, intratracheal or oral administration in rats, **dimethylarsinic acid** was distributed with the initially highest concentrations in the blood, muscles, kidneys, liver and lungs. The tissue concentrations of dimethylarsinic acid decreased very rapidly. However, in whole blood, about 12% to 22% of the administered dose was still detectable two days after intravenous, intratracheal or oral application, indicating redistribution from the serum into the erythrocytes (Stevens et al. 1977). In F344 rats, analysis of the arsenic concentration in plasma and the erythrocytes after the administration of 100 mg **dimethylarsinic acid**/kg diet for 3 days yielded an arsenic concentration in the erythrocytes which was 150 times higher than that in the plasma (Lu et al. 2004).

In mice, radioactivity was detected in various organs as early as 15 minutes after single oral doses of ^{14}C-labelled **dimethylarsinic acid**. After 24 hours, the radioactivity in the liver was between 1% and 2% of the administered dose; in the lungs, kidneys and bladder it was less than 0.05% (Hughes et al. 2008).

In hamsters given single oral doses, **dimethylarsinic acid** was distributed within 6 hours especially in the lungs, kidneys, spleen and liver, whereas the highest concentrations of the metabolite methylated to trimethylarsine were detected in the lungs, liver, kidneys and spleen (Yamauchi and Yamamura 1984).

In F344 rats given 0, 4, 40, 100 or 200 mg **dimethylarsinic acid**/kg diet (doses of about 0, 0.4, 4, 10 or 20 mg/kg body weight and day) for 14 days, the concentrations of the dimethylated and trimethylated arsenic compounds increased in a dose-dependent manner in the different tissues and in the urine. At the end of treatment, the concentrations of dimethylarsenic compounds in the blood, lungs, liver and kidneys were considerably higher than those of the trimethylarsenic compounds, whereas the concentrations of the trimethylarsenic compounds were higher in the bladder and urine (Adair et al. 2007).

A comparison of the distribution of dimethylarsenic compounds containing thiols and those not containing thiols in hamsters after intravenous injection showed that **dimethylarsinic acid** and **dimethyldithioarsinic acid** are distributed mainly in intact form throughout the organs and body fluids, whereas **dimethylarsinous acid** and **dimethylthioarsinic acid** are mostly bound to proteins. More than 60% of the administered dose of dimethylarsinous acid and dimethylthioarsinic acid was found in the muscles, liver, kidneys and lungs, but less than 4% in the erythrocytes (Naranmandura et al. 2010).

With methylarsonous acid and **dimethylarsinous acid**, the considerably higher binding affinity to rat haemoglobin compared with that to human haemoglobin (Lu

et al. 2004) and also the more pronounced complex formation of methylarsonic acid or **dimethylarsinic acid** with haemoglobin (Lu et al. 2007) were attributed to the longer persistence of organic arsenic compounds in the blood of rats. This difference is also explained by the fact that the haemoglobin of rats contains the reactive cysteine 13α, which is absent in humans (Lu et al. 2007).

3.1.3 Elimination

Monomethylarsenic compounds

After single oral doses of **methylarsonic acid** (0.5 mg arsenic), subjects eliminated 75% of the administered dose with the urine within 4 days (Buchet et al. 1981). Studies in B6C3F1 mice revealed that 8 hours after oral administration of **methylarsonic acid**, 80% was eliminated in the urine and faeces. After methylarsonic acid doses of 0.4 mg/kg body weight, urinary elimination was significantly greater than at 4.0 mg/kg body weight. The terminal half-liveswere not dose-dependent: between 4.2 and 4.9 hours for the liver, lungs and blood, 9.0 hours for the bladder and 15.9 hours for the kidneys (Hughes et al. 2005). In hamsters, 24 hours after the ingestion of **methylarsonic acid**, 27% of the administered dose was eliminated with the urine and 56% with the faeces. After intraperitoneal injection, 80% was eliminated with the urine and 1% with the faeces (Yamauchi et al. 1988). In sheep and goats, 85% and 90%, respectively, of the administered dose were recovered in the urine 72 hours after oral administration of **sodium methylarsonate** (Shariatpanahi and Anderson 1984).

Horses received intramuscular injections of 270 mg **disodium methylarsonate**/kg body weight and day for 5 days. The elimination of disodium methylarsonate from the blood and urine followed first-order kinetics, with half-lives of 44 and 38 hours, respectively. During the study and up to 4 days after the final treatment, up to 75% of the total arsenic dose was eliminated with the urine as dimethylarsinic acid. No other methylarsenic metabolites were detectable (Assis et al. 2008).

Dimethylarsenic compounds

Within 4 days after the ingestion of **dimethylarsinic acid**, subjects eliminated 78% to 80% of the dose unchanged with the urine (Buchet et al. 1981; Marafante et al. 1987). In mice and hamsters, after oral doses of **dimethylarsinic acid**, 56.4% and 38.7% of the dose were eliminated within 48 hours with the urine and 24.3% and 37.3% with the faeces, respectively. In mice and hamsters, respectively 7.7% and 11.2% were found in the form of dimethylarsinic acid complexes in the urine, and 4.9% and 3.9% in the faeces (Marafante et al. 1987). Higher values were obtained in another study with mice, in which 80.5% of the administered **dimethylarsinic acid** was eliminated with the urine and 15.8% with the faeces after 24 hours. In the three-phase elimination, 85% was eliminated with a half-time of 2.5 hours, about 14% with a half-time of 10 hours, and less than 0.5% with a half-time of 20 days (Vahter et al.1984). For rats, a different elimination pattern was found. Of the orally administered **dimethylarsinic acid**, 18.2% was found in the urine and 2.0% in the faeces during the first 24 hours, whereas during the following 24 hours 3.1% was found in the urine and 18.7% in the faeces. Elimination took place in two phases, whereby

45% of the dimethylarsinic acid was eliminated during the first phase with a half-life of about 13 hours, and 55% during the second phase with a half-life of 50 hours (Vahter et al.1984). After intravenous injection, and intratracheal and gavage administration of **dimethylarsinic acid** in rats, 71%, 60% and 25% were eliminated with the urine and 1.2%, 8% and 31% with the faeces within 24 hours. The half-lives for the three-phase elimination from the plasma after intravenous injection of 200 mg/kg body weight were 0.014, 0.217 and 3.42 hours. After oral, intravenous and intratracheal administration, the concentration in the plasma decreased to 50% within less than one hour. The clearance half-times from whole blood were given as 92, 76 and 90 days after intravenous, intratracheal and oral administration, respectively, and corresponded to the clearance half-lives from the erythrocytes of the rats. The considerably smaller amounts of dimethylarsinic acid eliminated after oral administration in rats compared with in other species was explained by the higher accumulation of dimethylarsinic acid in the erythrocytes, such as is known also in the case of inorganic arsenic (Stevens et al. 1977).

In hamsters, after oral administration of **dimethylarsinic acid**, 45% of the administered dose was found in the urine and 34.7% in the faeces over the following 24 hours (Yamauchi and Yamamura 1984).

After single oral doses of ^{14}C-labelled **dimethylarsinic acid**, radioactivity was detected in the urine of mice after only 15 minutes (Hughes et al. 2008).

One hour after the intravenous injection of **dimethylarsinic acid** or **dimethyldithioarsinic acid**, the substances were recovered from the urine mainly in intact form in hamsters, whereby over 70% of the administered dose was found, while less than 8% to 14% was found in the form of dimethylarsinic acid after treatment with **dimethylarsinous acid** and **dimethylthioarsinic acid** (Naranmandura et al. 2010).

Summary:

Methylarsenic compounds can be absorbed by inhalation, ingestion and through the skin. In rats and mice, about 80% of the methylarsonic acid or dimethylarsinic acid dose is absorbed after oral administration, rapidly distributed to the bladder, kidneys, lungs, liver, spleen, intestine and testes and eliminated mainly with the urine. In rats, accumulation in the erythrocytes was observed. Of the thioarsenic compounds, in particular dimethylthioarsinic acid is distributed throughout all organs.

3.2 Metabolism

Methylarsenic compounds can be methylated to the respective higher di-, tri- or tetramethylarsenic compounds. A diagram showing the metabolic pathways can be seen in Figure 1.

Although demethylation of dimethylarsinic acid in the intestine by microorganisms has been reported in rats (Chen et al. 1996; Yoshida et al. 1997), this could not be demonstrated in either humans (Buchet et al. 1981) or in rats (Buchet et al. 1981; Stevens et al. 1977), mice (Vahter et al. 1984) or hamsters (Marafante et al. 1987) and its likelihood was therefore excluded with a high probability (Yoshida et al. 2001). In a study with homogenates from different hamster tissues, the formation of ^{14}C-methylarsonous acid was demonstrated using ^{14}C-methylarsonic acid as the substrate for methylarsonic acid reductase (Sampayo-Reyes et al. 2000).

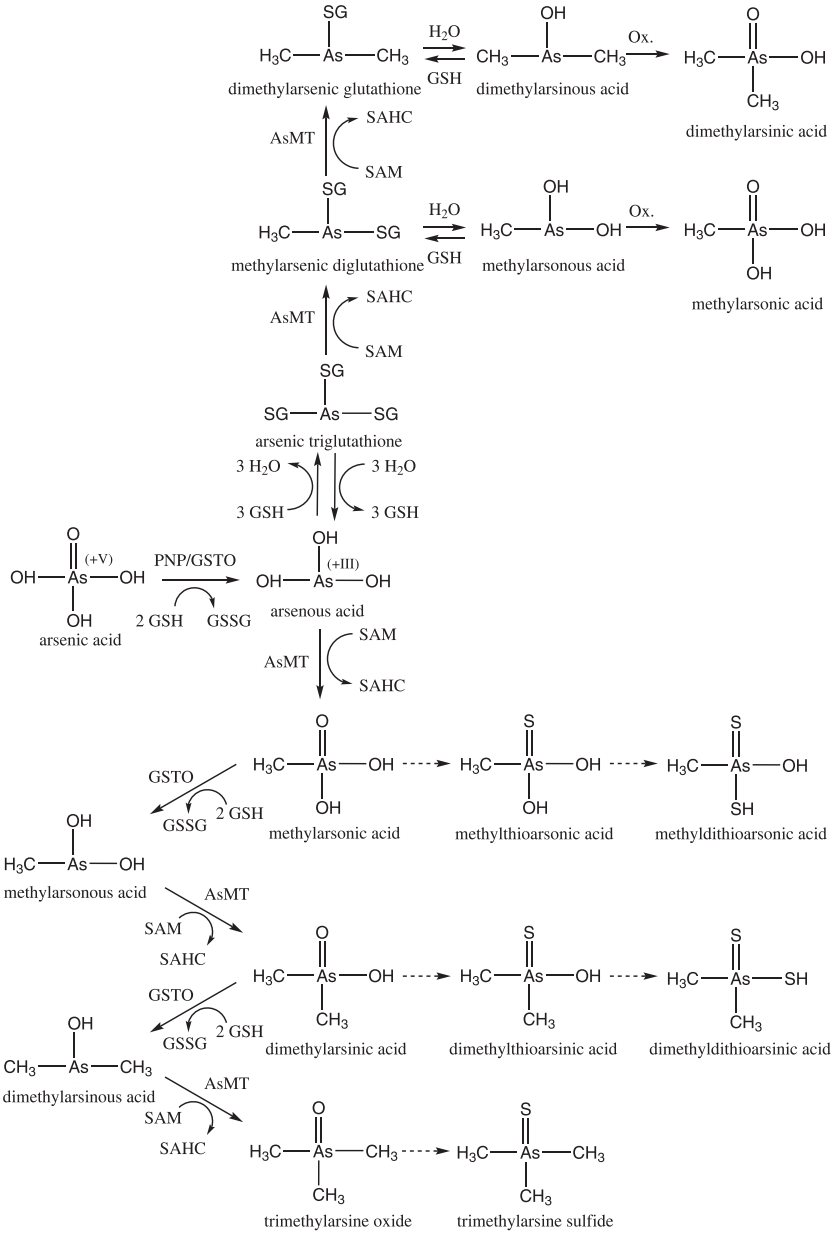


Figure 1 Metabolic pathways of arsenic (according to Pinyayev et al. 2011; Watanabe and Hirano 2013)
(AsMT: arsenic methyltransferase; GSH: glutathione; GSSG: oxidized glutathione; GSTO: glutathione S-transferase-omega; Ox.: oxidation; PNP: purine nucleoside-phosphorylase; SAM: S-adenosylmethionine; SAHC: S-adenosylhomocysteine)

Monomethylarsenic compounds

In the urine of subjects, the methylation of about 13% of the ingested **methylarsonic acid** to form dimethylarsinic acid (Buchet et al. 1981; Stevens et al. 1977) and of about 4% to form trimethylarsine oxide (Marafante et al. 1987) was determined.

The methylation is dependent on the duration of exposure. After exposures lasting 1 week or 7 months, 50.6% and 65.3% of the orally administered **methylarsonic acid** was determined as methylarsonic acid in the urine of rats, 19% and 27% as dimethylarsinic acid, 6.9% and 4.1% as trimethylarsine oxide, and 0.4% and 0.1% as the tetramethylarsonium ion, respectively (Yoshida et al. 1998).

In male and female rats given **methylarsonic acid** with the drinking water (methylarsonic acid doses of about 14 mg/kg body weight and day) for 12 weeks, the following concentrations of the different arsenic species were found in the urine: methylarsonic acid: 122–166 µg arsenic/ml (69.2%–79.2%), methylarsonous acid: 1.8–8.4 µg arsenic/ml (1.2%–3.5%), dimethylarsinic acid: 18–22 µg arsenic/ml (11.7%–9.2%), dimethylarsinous acid: 0.2–1.6 µg arsenic/ml (0.1%–1.7%), trimethylarsine: 0.1–0.4 µg arsenic/ml (0.01%–0.2%), trimethylarsine oxide: 4.8–4.9 µg arsenic/ml (2.0%–3.1%), and the tetramethylarsonium ion: 0.01–0.1 µg arsenic/ml. Three further metabolites found in several studies but not yet identified occurred in concentrations of up to 1.4 µg arsenic/ml (Shen et al. 2006).

In rats given **methylarsonic acid** with the drinking water in concentrations of 50 or 200 mg/l (methylarsonic acid doses of about 2 or 8 mg/kg body weight) for 60 weeks, 26.9% of the total arsenic compounds eliminated were found in the urine in the form of methylarsonic acid after 2 mg/kg body weight and 68.3% after 8 mg/kg body weight. The amount of dimethylarsinic acid eliminated with the urine was likewise found to be dose-dependent, but not, however, the amounts of trimethylarsine oxide, tetramethylarsonium ion and two other unidentified metabolites (Shen et al. 2003 a).

Within 24 hours after oral administration of ^{14}C-**methylarsonic acid** doses of 0.4 mg/kg body weight, mice eliminated 98.2% with the urine as the unchanged substance and 1.8% as methylarsonous acid. After oral administration of ^{14}C-**methylarsonic acid** doses of 40 mg/kg body weight, apart from methylarsonic acid (89.6%) and methylarsonous acid (1.2%) also the metabolites dimethylarsinic acid (6.2%), dimethylarsinous acid (1.1%) and trimethylarsine oxide (1.9%) were found in the urine (Hughes et al. 2005). Further studies with **methylarsonic acid** confirmed these results in mice after intravenous injection (determined in urine; Hughes and Kenyon 1998), in rats after ingestion (determined in bile; Cui et al. 2004) or intravenous injection (determined in urine; Suzuki et al. 2004) or also after oral administration or intravenous injection in hamsters (determined in urine; Yamauchi et al. 1988). In addition, in vitro studies with hepatocytes from humans or rats (Styblo et al. 1999) or with a human recombinant methyltransferase (Hughes et al. 2005) confirmed the methylation of methylarsonic acid. In hamsters treated with **methylarsonic acid**, < 1% of the eliminated methylarsonic acid was methylated to trimethylarsine (Yamauchi et al. 1988).

After oral administration of ^{14}C-**methylarsonous acid** doses of 0.4 mg/kg body weight, a quite different pattern of elimination was obtained in the 24-hour urine of mice: methylarsonic acid (6.3%), methylarsonous acid (0.6%) and especially the metabolites dimethylarsinic acid (81.5%), dimethylarsinous acid (10.9%), but only a small amount of trimethylarsine oxide (1.9%) were found (Hughes et al. 2005).

The marked methylation of **methylarsonous acid** to dimethylarsinic acid was determined also in vitro with rat hepatocytes (Styblo et al. 1999) or their cytosol (Styblo et al. 1995).

Dimethylarsenic compounds

After single oral doses of **dimethylarsinic acid**, 98% appeared unchanged in the urine of F344 rats after 2 hours. Within 24 hours, the amount of dimethylarsinic acid decreased steadily to 23.8%, whereas increasingly higher levels of trimethylarsine oxide (up to 56.8%) were found (Yoshida et al. 1997). In mice, after single oral doses of **dimethylarsinic acid**, the metabolites dimethylarsinous acid, trimethylarsine oxide, dimethylthioarsinic acid and trimethylarsine sulfide were detected in the urine after 24 hours. After the administration of **dimethylarsinous acid**, trimethylarsine oxide, dimethylthioarsinic acid and trimethylarsine sulfide were found as urinary metabolites (Hughes et al. 2008). In hamsters, after single oral doses of **dimethylarsinic acid**, 67.9% of the dose was determined as dimethylarsinic acid and 32.0% as trimethylarsine in the urine within 24 hours. In the faeces, analysis revealed almost exclusively dimethylarsinic acid, but no trimethylarsine (Yamauchi and Yamamura 1984).

Within 48 hours after oral administration of **dimethylarsinic acid**, 3.5% trimethylarsine oxide was found in the urine of mice and up to 6.4% in that of hamsters (Marafante et al. 1987).

When **dimethylarsinic acid** was administered with the drinking water to rats, after 1 week and after 7 months, 0.1% and 0.1% of the administered dose was found in the urine as methylarsonic acid, 44.9% and 60.7% as dimethylarsinic acid, 40.0% and 23.9% as trimethylarsine oxide, 0.4% and 0.6% as the tetramethylarsonium ion, and 0.8% and 0.2% as arsenobetaine, respectively (Yoshida et al. 1998). After administration of **dimethylarsinic acid** with the drinking water (dimethylarsinic acid doses of about 14 mg/kg body weight and day) for 12 weeks, the following arsenic species were found in the urine of male and female rats: methylarsonic acid: 0.1–0.2 µg arsenic/ml, methylarsonous acid: not detectable – 0.5 µg arsenic/ml, dimethylarsinic acid: 40–41 µg arsenic/ml (41.2%–57.7%), dimethylarsinous acid: 0.4–0.7 µg arsenic/ml, trimethylarsine: 0.2–2.3 µg arsenic/ml and trimethylarsine oxide: 23–39.7 µg arsenic/ml (23.7%–55.9%) and tetramethylarsonium ion: 0.1–1.0 µg arsenic/ml. Three unidentified metabolites occurred at concentrations of up to 7.1 µg arsenic/ml (Shen et al. 2006).

In F344 rats given **dimethylarsinic acid** doses of up to 200 mg/kg body weight and day with the diet for 14 days, among the dimethylated and trimethylated arsenic compounds also dimethylthioarsinic acid and trimethylarsine sulfide were eliminated with the urine in a dose-dependent fashion (Adair et al. 2007).

Trimethylarsenic compounds

Following the administration of **trimethylarsine oxide** with the drinking water, urinalysis revealed that after 1 week and after 7 months 0.4% and 0.6%, respectively, of the administered dose was present as methylarsonic acid, 1.9% and 6.6% as dimethylarsinic acid, 89.4% and 88.9% as trimethylarsine oxide, and 5.1% and 2.6% as the tetramethylarsonium ion (Yoshida et al. 1998). After the administration of **trimethyl-**

arsine oxide with the drinking water (trimethylarsine oxide doses of about 14 mg/kg body weight and day) for 13 weeks, the following arsenic species were found in the urine of male and female rats: methylarsonic acid: not detectable – 0.03 µg arsenic/ml, methylarsonous acid: not detectable – 0.05 µg arsenic/ml, dimethylarsinic acid: 0.1–0.3 µg arsenic/ml, dimethylarsinous acid: 0.02 µg arsenic/ml, trimethylarsine: 5–17 µg arsenic/ml and trimethylarsine oxide: 239–292 µg arsenic/ml, tetramethylarsonium ion: 2.9–9.7 µg arsenic/ml. Three other unidentified metabolites occurred in concentrations of up to 27 µg arsenic/ml (8.2%) (Shen et al. 2006).

After the administration of **trimethylarsine oxide** with the drinking water for 60 weeks, trimethylarsine oxide, dimethylarsinic acid, the tetramethylarsonium ion, arsenobetaine, and one unidentified arsenic metabolite were found in the urine (Shen et al. 2003 b).

Thiomethylarsenic compounds

The also identified organic thioarsenic compounds **methylthioarsonic acid**, **dimethylthioarsinic acid**, **dimethyldithioarsinic acid** (Suzuki et al. 2007) or **trimethylarsine sulfide** (Adair et al. 2007) can be formed in erythrocytes or other cells (Naranmandura and Suzuki 2008; Naranmandura et al. 2007 a) and in the gastrointestinal tract by hydrogen sulfide-producing micro-organisms that replace the oxygen of the methylarsenic compounds with sulfur (Kubachka et al. 2009; Pinyayev et al. 2011). Organic thioarsenic compounds were found in the urine of humans (Chilakapati et al. 2010; Raml et al. 2007), sheep (Hansen et al. 2004), hamsters (Naranmandura et al. 2007 b) and rats (Naranmandura et al. 2007 b; Suzuki et al. 2010; Yoshida et al. 1997) after exposure to inorganic arsenic compounds.

As studies have shown that dimethylarsinous acid is very unstable in aqueous solutions and difficult to determine, it is assumed that in most of the studies **dimethylthioarsinic acid** was incorrectly identified as dimethylarsinous acid (Hansen et al. 2004; Naranmandura et al. 2007 a, b).

Comparison of the various methylarsenic compounds

A comparison of different methylarsenic compounds (Shen et al. 2006, Table 1) shows that more than 80% of methylarsonous acid is methylated to form dimethylarsinic acid, whereas the other methylarsenic compounds are eliminated mainly in unchanged form or are methylated to the next-higher di-, tri- or tetramethylarsenic compound in amounts, for example, of 10% (methylarsonic acid), 40% (dimethylarsinic acid) or 2% (trimethylarsine oxide, not given in the table).

Summary:

The methylarsenic compounds are methylated to higher dimethylarsenic or trimethylarsenic compounds or converted to thiomethylarsenic compounds. More than 80% of the methylarsonous acid is methylated to dimethylarsinic acid, about 10% of the methylarsonic acid to dimethylarsinic acid, 40% of the dimethylarsinic acid to trimethylarsine oxide and 2% of the trimethylarsine oxide to the tetramethylarsonium ion (see Table 1).

Table 1 Methylarsenic species in the urine of rats after the administration of various methylarsenic compounds

Administered substance	Species	Methylarsenic species in the urine			References
		Methylarsonic acid	Dimethylarsinic acid	Trimethylarsine oxide	
methylarsonous acid[a] (1 × oral)	mouse (♀)	6.3%	81.5%	1.9%	Hughes et al. 2005
methylarsonic acid[b] (in the drinking water, 12 weeks)	rat (♀ and ♂)	74.2%	10.5%	2.6%	Shen et al. 2006
dimethylarsinic acid[b] (in the drinking water, 12 weeks)	rat (♀ and ♂)	≤ 0.2%	49.5%	40.0%	Shen et al. 2006
trimethylarsine oxide[b] (in the drinking water, 12 weeks)	rat (♀ and ♂)	–	≤ 0.1%	88.5%	Shen et al. 2006

[a] % related to the administered dose;
[b] % related to the total arsenic level in the urine

4 Effects in Humans

4.1 Single exposures

4.1.1 Inhalation

A man who sprayed a mixture of **sodium dimethylarsinate** and **dimethylarsinic acid** from the loading flap of his pickup truck with a manual sprayer without safety equipment suffered from nausea after about two hours. Analysis of the blood did not yield any unusual findings (Peoples et al. 1979).

After the mixing, loading and application of a pesticide consisting of **sodium dimethylarsinate** and **dimethylarsinic acid**, a man developed stomach ache after a certain time (Peoples et al. 1979).

In one person, headaches and later dizziness, weakness, nausea and stomach cramps occurred immediately after wiping up a mixture of **sodium dimethylarsinate** and **dimethylarsinic acid** (Peoples et al. 1979).

4.1.2 Ingestion

Liquid **sodium methylarsonate** was sprayed onto the clothing of an employee when he detached a hosepipe from its atomizer spraying head, and it was also sprayed into his mouth. Despite spitting the liquid out and immediately rinsing his mouth with water, the man later developed stomach cramps. On the way to hospital

symptoms of paresis occurred, together with irregular respiration and loss of consciousness. The findings obtained in the clinic after blood, urine and organ examinations were not given. After five days, the man was free of symptoms (Peoples et al. 1979).

4.1.3 Dermal absorption

Numerous pesticide users (no other details) who spilt **sodium dimethylarsinate** and **dimethylarsinic acid** over their skin have reported contact dermatitis, but never systemic symptoms (Peoples et al. 1979).

4.2 Repeated exposure

In forestry workers who used **sodium methylarsonate** and **disodium methylarsonate** without protective clothing and were exposed mainly via the skin, arsenic levels of up to 1 µg arsenic/l urine were determined at the end of the working week. The medical examinations did not reveal any substance-related diseases (Peoples et al.1979).

4.3 Local effects on skin and mucous membranes

Skin

A herbicide sprayer, who had worn gloves while spraying a mixture of **sodium dimethylarsinate** and **dimethylarsinic acid**, experienced pain five days after the exposure and the epidermis of both palms of his hands peeled off (Peoples et al. 1979).

A powder consisting of **sodium dimethylarsinate** and **dimethylarsinic acid** blown directly into the face of a man resulted in skin eruption, which within six days had worsened and was characterized as erythematous and oedematous dermatitis (Peoples et al. 1979).

An agricultural labourer into whose neck weeds were blown which had been sprayed with a mixture of **sodium methylarsonate**, **dimethylarsinic acid** and **sodium dimethylarsinate**, developed pruritic dermatitis in the contact area (Peoples et al. 1979).

Skin rashes developed on the arms or legs of two persons who had been exposed to **sodium dimethylarsinate** or another organic arsenic compound (no other details); in each case these were evaluated as contact dermatitis (Peoples et al. 1979).

Eyes

A man who sprayed a mixture of **sodium dimethylarsinate** and **dimethylarsinic acid** into his left eye suffered from conjunctival and corneal irritation (no other details), despite immediately washing the substance out with water. Also several other persons whose eyes had come into contact either with the same mixture or **sodium methylarsonate** reported irritation of the eyes (Peoples et al. 1979).

In addition, other cases of irritative conjunctivitis or irritation of the eyes have been described in forestry or agricultural workers after exposure to **sodium dime-**

thylarsinate, **dimethylarsinic acid** or other methylarsenic compounds (Peoples et al. 1979).

4.4 Allergenic effects

Sensitizing effects on the skin

In a 26-year-old woman occupationally exposed to **dimethylarsinic acid**, who had developed dermatitis on her face possibly caused by airborne contact with the substance, patch tests with 0.1% and 1% dimethylarsinic acid in water yielded a 2+ reaction after 3 days. No reaction to these preparations was obtained in a control person (Bourrain et al. 1998).

In addition, sporadic reports of possibly allergic reactions to methylarsenic compounds are available, in which, however, no details are given as to whether patch tests or other diagnostic measures were performed: In an agricultural worker, a skin eruption spreading over his arms and legs was evaluated as allergic dermatitis one month after exposure to a mixture of organic arsenic compounds (no other details) (Peoples et al. 1979). Although an employee had sprayed a mixture of **sodium dimethylarsinate** and **dimethylarsinic acid** for only a few minutes in the morning, he developed a generalized pruritic eruption during the afternoon; this was evaluated as a possible allergic reaction (Peoples et al. 1979). Another employee developed dermatitis one day after spraying **dimethylarsinic acid** in hot, windy weather. The physician who treated him assessed this to be an allergic reaction (Peoples et al. 1979).

Sensitizing effects on the airways

There are no data available.

4.5 Reproductive and developmental toxicity

There are no data available.

4.6 Genotoxicity

There are no data available.

4.7 Carcinogenicity

There are no data available for organic arsenic compounds. However, arsenic and the inorganic arsenic compounds converted to methylated arsenic compounds are carcinogenic in humans. Increased risks of cancer were determined after inhalation exposure to arsenic for the lungs and after ingestion for the bladder, kidneys, skin and lungs (documentation "Arsenic and its inorganic compounds (with the exception of arsine)" 2005).

5 Animal Experiments and in vitro studies

5.1 Acute toxicity

5.1.1 Inhalation

A 2-hour LC_{50} of 3900 mg **dimethylarsinic acid**/m^3 was calculated for female Sherman rats after exposure in whole-body chambers. Male rats were less sensitive with an LC_{50} of more than 6900 mg dimethylarsinic acid/m^3. In male and female Swiss Webster mice, an LC_{50} of more than 6400 mg **dimethylarsinic acid**/m^3 was obtained. Respiratory distress, rhinitis and encrustations around the eyes have been described as symptoms of intoxication in rats and mice. After exposure, diarrhoea and decreased body weight gains were observed within 14 days. Necropsy of the animals that died revealed bright red lungs with dark spots and a caecum filled with solid intestinal content (Stevens et al. 1979).

The 2-hour LC_{50} for **disodium methylarsonate** (whole-animal exposure chambers) was more than 6100 mg/m^3 in male and female Sherman rats and more than 6900 mg disodium methylarsonate/m^3 in male and female Swiss Webster mice. During exposure, the animals suffered from respiratory distress, but recovered rapidly thereafter. In the exposure chamber, the concentrations of dimethylarsinic acid or disodium methylarsonate were so high that the animals were hardly visible (Stevens et al. 1979).

For sensory irritation, RD_{50} values (decrease in respiration rate by 50%) of 3150 mg **dimethylarsinic acid**/m^3 and 1540 mg **disodium methylarsonate**/m^3 were calculated in mice (Stevens et al. 1979).

5.1.2 Oral administration

In rats, LD_{50} values of about 1000 mg/kg body weight were calculated for **methylarsonic acid** and **sodium methylarsonate**, and of about 700 mg/kg body weight for **dimethylarsinic acid** and **disodium methylarsonate**. In rabbits, hares and cattle the LD_{50} values were 102, 173 and 250 mg/kg body weight, indicating much higher sensitivity to **sodium methylarsonate** than in rats (see Table 2).

The administration of **methylarsonic acid**, **dimethylarsinic acid** and **trimethylarsine oxide** caused decreased motility and laboured breathing in mice. After the administration of **trimethylarsine oxide**, the animals' breath had an odour resembling that of garlic for a short period (Kaise et al. 1989).

5.1.3 Dermal application

In rabbits, the LD_{50} for **sodium methylarsonate** was between 2000 and 4000 mg/kg body weight after exposure for 24 hours and a 2-week recovery period (US EPA 1975). Further dermal LD_{50} values for **dimethylarsinic acid**, **sodium methylarsonate** and **disodium methylarsonate** were given as being more than 2000 mg/kg body weight (no other details) in rabbits (US EPA 2006).

Table 2 Studies of acute toxicity after oral administration

Species	LD_{50} [mg/kg body weight]	References
methylarsonic acid		
rat	961–1101	Gaines and Linder 1986
mouse	1800	Kaise et al. 1989
sodium methylarsonate		
rat	1000	Peoples et al. 1979
	1800	Jaghabir et al. 1988
	1059–1105	Gaines and Linder 1986
mouse	300	Judd 1979
	1200	Kaise et al. 1989
rabbit	102	Jaghabir et al. 1988
hare	173	Exon and Harr 1974
cattle	250	Jaghabir et al. 1988
disodium methylarsonate		
rat	700	Peoples et al. 1979
	821–928	Gaines and Linder 1986
dimethylarsinic acid		
rat	700	Peoples et al. 1979
	644–1315	Gaines and Linder 1986
trimethylarsine oxide		
mouse	10 600	Kaise et al. 1989

5.1.4 Intraperitoneal injection

After intraperitoneal injection, the LD_{50} for **dimethylarsinic acid** in male and female Sherman rats was 720 and 520 mg dimethylarsinic acid/kg body weight and in male and female Swiss Webster mice 520 and 600 mg dimethylarsinic acid/kg body weight, respectively. For **disodium methylarsonate**, LD_{50} values of 600 and 561 mg disodium methylarsonate/kg body weight were determined for male and female Sherman rats and 600 and 681 mg disodium methylarsonate/kg body weight for male and female Swiss Webster mice, respectively. The animals died within 4 days. The symptoms of intoxication were ruffled fur, laboured breathing, hunched posture, loss of the neck reflex, a decrease in body temperature and immobility. Gross-pathological examinations revealed a small red thymus, bright lungs, dark discoloration of the adrenal glands, liver and spleen, the caecum filled with solid intestinal content, irritation of the gastric mucosa, and blood and mucus in the intestine (Stevens et al. 1979).

The LD_{50} for **methylarsonous acid** after intraperitoneal administration in hamsters was 29.3 µmol/kg body weight (3.7 mg/kg body weight) (Petrick et al. 2001).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

In a 90-day inhalation study (see Table 3), cellular changes in the form of intracytoplasmic eosinophilic globules were found in the epithelium of the nasal turbinates of male and female Sprague-Dawley rats at 34 mg **dimethylarsinic acid**/m³ and above. These changes were interpreted as the accumulation of secretory proteins or as an adaptive response to irritation of the upper respiratory tract. The diffuse effects on different blood cells and the increased haematocrit value were not considered relevant and the nodules on the epididymides occurring only at 10 and 34 mg/m³ were not discussed (Luxembourg Industries 1994 a).

5.2.2 Oral administration

The results of the studies with repeated oral administration of methylarsenic compounds are shown in Table 4.

Methylarsonic acid

In 2-year studies with rats, urinary bladder hyperplasia occurred after methylarsonic acid doses of about 2.5 mg/kg body weight and day and above and the incidence of glutathione S-transferase placental form positive foci was significantly increased in the liver at about 10 mg/kg body weight and day (Shen et al. 2003 a). Diarrhoea, emaciation and dehydration occurred at methylarsonic acid doses of about 20 mg/kg body weight and day and above.

Table 3 Effects of dimethylarsinic acid after repeated inhalation

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 10 ♂, 10 ♀	**13 weeks**, 0, 10, 34 or 100 mg **dimethylarsinic acid**/m³, 6 hours/day, 6 days/week, head/nose exposure	**10 mg/m³**: ♀: haematocrit value ↑, gross-pathological findings in ♂: nodules on epididymides (2/10); **34 mg/m³**: ♀: haematocrit value ↑, ♂: leukocytes ↓ and eosinophilic granulocytes ↑, ♀: urea nitrogen ↑, ♂: nodules on epididymides (2/10); **34 mg/m³ and above**: ♀ and ♂: epithelium of the nasal turbinates: intracytoplasmic eosinophilic globules; **100 mg/m³**: ♀: MCH ↓ and lymphocytes ↓; no substance-related mortality, no changes in organ weights	Luxembourg Industries 1994 a

MCH = mean corpuscular haemoglobin

Table 4 Effects of methylarsenic compounds after repeated oral uptake

Species, strain, number per group	Exposure	Findings	References
methylarsonic acid			
rat, F344, 25 ♂	**5, 10, 15 or 20 days**, 0 or 200 mg **methylarsonic acid**/kg diet (about 0 or 20 mg methylarsonic acid/kg body weight and day), purity: 99.9%	**about 20 mg/kg body weight**: NOAEL (liver and bladder), induction of various Phase I and II enzymes	Kinoshita et al. 2007 b
rat, F344, 3 ♂ and 3 ♀	**13 weeks**, 0 or 187 mg **methylarsonic acid**/l drinking water (about 0 or 14 mg methylarsonic acid/kg body weight and day), purity: > 98%	**about 14 mg/kg body weight**: no effects on absolute and relative kidney and liver weights, blood parameters, activities of AST, ALT, AP and γ-GT, blood urea nitrogen, bladder (electron microscopic examination of bladder only)	Shen et al. 2006
rat, F344, no other details	**13 weeks**, 0, 10, 100, 500 or 1250 mg **methylarsonic acid**/kg diet (about 0, 0.75, 7.5, 37.5 or 94 mg methylarsonic acid/kg body weight and day), purity: 98.9%–99.8%	**about 37.5 mg/kg body weight and above**: body weight gains ↓, drinking water consumption ↑	Arnold et al. 2003
rat, F344, 60 ♂ and 60 ♀	**104 weeks**, 0, 50 or 200 mg **methylarsonic acid**/l drinking water (about 0, 2.5 or 10 mg methylarsonic acid/kg body weight and day)	**about 2.5 mg/kg body weight and above**: bladder: hyperplasia; **about 10 mg/kg body weight**: liver: incidence of GST-P positive foci ↑; no significant differences in body weight gains, food and water intake, mortality, the relative weights of the liver, spleen and kidneys, incidences of benign and malignant tumours, serum values: leukocyte and erythrocyte count, activities of AST and ALT, blood urea and total protein	Shen et al. 2003 a

Table 4 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, F344, 60 ♂ and 60 ♀	**108 weeks**, 0, 50 or 400 mg **methylarsonic acid**/kg diet (about 0, 2.5 or 20 mg methylarsonic acid/kg body weight and day), purity: 98.9%–99.8%	**0 mg/kg body weight**: mortality: ♂: 42%, ♀: 18%; **about 2.5 mg/kg body weight**: mortality: ♂: 50%, ♀: 33%, NOAEL; **about 20 mg/kg body weight**: mortality: ♂: 45%, ♀: 22%, body weight gains ↓, drinking water consumption ↑, diarrhoea, at end of study: emaciation and dehydration; blood: ♂: activities of AP, AST and γ-GT ↓, creatinine and cholesterol ↓; organ weights: ♀: absolute and relative weights of kidneys, heart and liver ↑, ♂ and ♀: absolute brain and thyroid weights ↓; gastrointestinal tract: thickened wall, mucosa: oedematous, congested, haemorrhagic, necrotic, ulcerated or perforated, serosa: congested, lumen: distended with foamy, mucous or haemorrhagic contents, intestinal loops adhering to each other or to neighbouring organs; intestine: number of rectal goblet cells ↑, squamous cell metaplasia in caecum, colon and rectum, mucosa with desquamated epithelial cells, vascular congestion and inflammation; small intestine with inflammation and perforating ulcerations, peritonitis with serous atrophy of fat pads in abdominal wall and cavity; inflammation in the ureter, bladder, kidneys, uterus, prostate, testes, epididymides, seminal vesicles is possibly a secondary effect of the perforating ulcers in the gastrointestinal tract or of released intestinal contents	Arnold et al. 2003; Luxembourg Industries 1990

Table 4 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, F344, 60 ♂ and 60 ♀	**108 weeks**, 1300 mg **methylarsonic acid**/kg diet (about 65 mg methylarsonic acid/kg body weight and day) → after week 53: 1000 mg **methylarsonic acid**/kg diet (about 50 mg methylarsonic acid/kg body weight and day) → after week 60: 800 mg **methylarsonic acid**/kg diet (about 40 mg methylarsonic acid/kg body weight and day), purity: 98.9%–99.8%	**about 65 mg/kg body weight**: due to high mortality → reduction to 50 or 40 mg/kg body weight; **about 65/50/40 mg/kg body weight**: mortality: ♂: 67%, ♀: 35%; body weight gains ↓ although food intake ↑, drinking water consumption ↑, diarrhoea; blood: glucose, total protein, albumin ↓, ♀: activity of AST ↓, cholesterol ↓; urine: volume, specific gravity and pH ↓; organ weights: ♂ and ♀: relative heart weights ↑, absolute brain weights ↓; ♀: adrenal glands: focal hyperplasia and congestion, liver: focal histiocytic proliferation; no neoplasms	Arnold et al. 2003; Luxembourg Industries 1990
mouse, B6C3F1, 12 ♂ and 12 ♀	**14 weeks**, 0, 10, 100, 500 or 1250 mg **methylarsonic acid**/kg diet (♂: 0, 2.1, 22.5, 110.6 or 288.6 mg methylarsonic acid/kg body weight and day; ♀: 0, 2.8, 27.5, 137.4 or 342.5 mg methylarsonic acid/kg body weight and day), purity: > 99.8%	**288.6/342.5 mg/kg body weight**: no unusual findings with regard to mortality, food intake, absolute body weights, differential blood count, gross-pathological and histopathological findings or organ weights (no other details)	US EPA 2006
mouse, B6C3F1, no other details	**42 weeks**, 0, 1100 or 1800 mg **methylarsonic acid**/kg diet (about 0, 137.5 or 225 mg methylarsonic acid/kg body weight and day), purity: 98.9%–99.8%	**about 137.5 mg/kg body weight and above**: mortality ↑; no data as to whether lower doses tested or not; dose-dependent changes in intestine: squamous cell metaplasia and chronic inflammation, adrenal cortex: thickening and hyperplasia	Arnold et al. 2003

Table 4 (continued)

Species, strain, number per group	Exposure	Findings	References
mouse, B6C3F1, 52 ♂ and 52 ♀	**104 weeks**, 0, 10, 50, 200 or 400 mg **methylarsonic acid**/kg diet (about 0, 1.25, 6.25, 25 or 50 mg methylarsonic acid/kg body weight and day), purity: 98.9%–99.8%	**about 6.25 mg/kg body weight and above**: food intake ↑, soft, slimy faeces; **about 25 mg/kg body weight and above**: drinking water consumption ↑; **about 50 mg/kg body weight**: body weight gains ↓, weights of heart, spleen and kidneys ↓, metaplasia in caecum, colon, rectum; kidneys: nephropathy and nephrocalcinosis; thyroid: follicular cell hyperplasia; no neoplasms	Arnold et al. 2003
dog, Beagle, 5 ♂ and 5 ♀	**52 weeks**, 0, 2, 8 or 35 mg **methylarsonic acid**/kg body weight and day, in gelatine capsules, 6 days/week, purity: 99.8%	**2 mg/kg body weight**: NOAEL; **8 mg/kg body weight and above**: ♀: body weight gains ↓, vomiting, diarrhoea, salivation, ♀: relative kidney weights ↑; **35 mg/kg body weight**: unkempt coat with lack of gloss, ♂: body weight gains ↓, emaciation, ♀: oestrous frequency ↓, ♀: plasma: total protein and cholesterol ↓, ♂: urine: specific gravity ↑; relative weight: hearts ↑, ♂: adrenal glands and liver ↑; ♀: liver: glycogen ↓, ovaries: absence of corpora lutea, kidneys: fat vacuoles in the corticomedullary region	Luxembourg Industries 1988
sodium methylarsonate			
rabbit, New Zealand White, 2–4 ♂	**40 days**, 0, 5, 10 or 20 mg **sodium methylarsonate**/kg body weight and day	**5 mg/kg body weight and above**: dose-dependent findings in the intestine: distended; liver: hyperaemia, degeneration of hepatocytes, inflammation in the periportal area; kidneys: swollen, tubular necrosis, interstitial nephritis, vascular hyperaemia; symptoms reversible	Jaghabir et al. 1988, 1989

Table 4 (continued)

Species, strain, number per group	Exposure	Findings	References
rabbit, New Zealand White, 2 ♂ and 2 ♀, controls: 1 ♂ and 1 ♀	**2, 4, 7, 12, 17, 36 or 52 weeks**, 0 or 50 mg **sodium methylarsonate**/kg diet (about 0 or 1.5 mg sodium methylarsonate/kg body weight and day)	**about 1.5 mg/kg body weight**: only after 7 or 12 weeks: liver inflammation (8/8 animals), partly with reactive hyperplasia; no abnormal findings in other organs	Exon and Harr 1974
rabbit, New Zealand White, 2 ♂ and 2 ♀	**12 weeks**, 0 or 50 mg **sodium methylarsonate**/kg diet (about 0 or 1.5 mg sodium methylarsonate/kg body weight and day), recovery period: 5 or 13 weeks	**about 1.5 mg/kg body weight**: no abnormal findings	Exon and Harr 1974
cattle, White-faced, aged 1 year, 2 cows, 3 bulls, control animals: 2 bulls	**10 days**, 10 mg **sodium methylarsonate**/kg body weight and day	**10 mg/kg body weight**: mortality (1/5), body weights ↓, pronounced diarrhoea, dehydration, lethargy; liver: multiple foci of coagulative necrosis; kidneys: swollen, darkened and haemorrhagic medulla, nephrosis; stomach: haemorrhagic gastritis	Dickinson 1972

Table 4 (continued)

Species, strain, number per group	Exposure	Findings	References
dimethylarsinic acid			
rat, F344, 7 ♀	**6 hours to 10 weeks**, 0 or 100 mg **dimethylarsinic acid**/kg diet (about 0 or 10 mg dimethylarsinic acid/kg body weight and day)	6 hours: **about 10 mg/kg body weight**: bladder: small punctate lesions in the luminal surface epithelium; 24 hours: **about 10 mg/kg body weight**: bladder: exfoliation of the superficial cells, time-dependent focal necrosis and cellular exfoliation; 3 days: **about 10 mg/kg body weight**: water intake ↑, urine: creatinine ↓; 7 days: **about 10 mg/kg body weight**: bladder: luminal surface urothelial cells: ropy microvilli, pitting, necrosis, exfoliation, labeling index (2× above controls): acc. to authors more probably initial regeneration than mitogenic effect; 2 weeks: **about 10 mg/kg body weight**: bladder: cytotoxicity and necrosis, proliferations (6× above controls); 4 weeks: **about 10 mg/kg body weight**: urine: quantity ↑, creatinine ↓, Ca^{2+} ↑; 10 weeks: **about 10 mg/kg body weight**: water intake ↑; bladder: absolute and relative weights ↑, hypertrophy, pronounced cytotoxicity, extensive cellular necrosis, decreased proliferations (3× above controls); kidneys: absolute and relative weights ↑, calcifications	Cohen et al. 2001
rat, F344, 25 ♂	**5, 10, 15 or 20 days**, 0 or 200 mg **dimethylarsinic acid**/kg diet (about 0 or 20 mg dimethylarsinic acid/kg body weight and day), purity: 98%	**about 20 mg/kg body weight**: total level of cytochrome P450 ↑ only after 10 days, relative liver weights ↑ after 20 days, bladder: cell proliferation and apoptosis ↑, induction of various Phase I and Phase II enzymes	Kinoshita et al. 2007 b

Table 4 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, F344, 10 ♀	**2 weeks**, 0 or 100 mg **dimethylarsinic acid**/kg diet (about 0 or 10 mg dimethylarsinic acid/kg body weight and day), purity: 99.5%, ± 560 mg 2.3-dimercaptopropane-1-sulfonic acid/kg body weight	**about 10 mg/kg body weight**: vesicular epithelium: cytotoxicity and regenerative hyperplasia – demonstrated by light and electron microscope – inhibited by co-administration of the chelator for trivalent arsenic compounds; urine: concentrations of dimethylarsinic acid (66.4 µM) and trimethylarsine oxide (73.2 µM) were 507 µM and 2.8 µM, respectively, after simultaneous administration of the chelator → inhibition of the formation of trimethylarsine oxide via trivalent dimethylarsinous acid (see Figure 1) ⇒ the dimethylarsinous acid formed after the administration of dimethylarsinic acid causes the toxic effects	Cohen et al. 2002
rat, NBR, 10 ♂	**4 weeks**, 0, 5, 10 or 20 mg **dimethylarsinic acid**/kg body weight and day, 5 days/week, gavage	**5 mg/kg body weight and above**: kidneys: cell proliferation ↑; **10 mg/kg body weight and above**: kidneys: 8-OHdG formation (see Section 5.6.2) ↑, proximal tubular cells: vacuolar degeneration and dilation	Vijayaraghavan et al. 2001
rat, F344, 10 ♂ and 10 ♀	**4 weeks**, 0, 57, 85 or 113 mg **dimethylarsinic acid**/kg body weight and day	**57 mg/kg body weight and above**: mortality due to nephropathy ↑, kidneys: proximal tubular necrosis and degeneration and hyperplasia of the epithelium covering the papillae, caecum: ulcerative, colitis-like changes; effects more pronounced in ♀	Murai et al. 1993
rat, F344, 10 ♂	**4 weeks**, 0 or 200 mg **dimethylarsinic acid**/l drinking water (about 0 or 30 mg dimethylarsinic acid/kg body weight and day)	**about 30 mg/kg body weight**: at the beginning of treatment 6-week-old animals: mortality 10/10, 8-week-old animals: mortality 1/10, 10-week-old animals: mortality 0/10	Wanibuchi et al. 1996

Table 4 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, F344, 12 ♂	**8 weeks**, 0, 10, 25 or 100 mg **dimethylarsinic acid**/l drinking water (about 0, 1.5, 3.75 or 15 mg dimethylarsinic acid/kg body weight and day)	**about 1.5 mg/kg body weight and above**: bladder: dose-dependent proliferation of surface epithelial cells; **15 mg/kg body weight**: mortality (5/10), body weight gains ↓, liver: necrosis and fatty degeneration in hepatocytes surrounding central vein; no other organs examined	Wanibuchi et al. 1996
rat, F344, 10 ♀	**10 weeks**, 0, 2, 10, 40 or 100 mg **dimethylarsinic acid**/kg diet (Purina 5002), (about 0, 0.15, 0.75, 3 or 7.5 mg dimethylarsinic acid/kg body weight and day), purity: 98.9%–100%	**about 0.15 mg/kg body weight and above**: absolute and relative kidney weights ↑, dose-dependent calcification in corticomedullary region; **about 3 mg/kg body weight and above**: food and water intake ↑, urine: quantity ↑, creatinine and electrolytes ↓ but Ca^{2+} ↑; bladder: relative weights ↑, hyperplasia, proliferation; **about 7.5 mg/kg body weight**: bladder epithelium: marked necrosis and vacuolar degeneration, surface epithelium with exfoliation and accumulation of small, round cells with pleomorphic microvilli; in the lumen: exfoliated epithelium and blood; ♀ more sensitive than ♂	Arnold et al. 1999
rat, F344, 10 ♀	**10 weeks**, 0 or 100 mg **dimethylarsinic acid**/kg diet (Altromin) (about 0 or 7.5 mg dimethylarsinic acid/kg body weight and day)	**about 7.5 mg/kg body weight**: bladder: same type of damage, but less pronounced than with the Purina 5002 diet	Arnold et al. 1999

Table 4 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, F344, 10 ♂	**10 weeks**, 0 or 100 mg **dimethylarsinic acid**/kg diet (Purina 5002) (about 0 or 7.5 mg dimethylarsinic acid/kg body weight and day)	**about 7.5 mg/kg body weight**: water intake ↑, urine: quantity ↑, creatinine and electrolytes ↓ but Ca^{2+} ↑; bladder: weights ↑, proliferation, kidneys: absolute and relative weights ↑, calcification in medulla; in total: fewer effects than in ♀	Arnold et al. 1999
rat, F344, 10 ♀	**10 weeks**, 0 or 100 mg **dimethylarsinic acid**/l drinking water (about 0 or 7.5 mg dimethylarsinic acid/kg body weight and day)	**about 7.5 mg/kg body weight**: bladder epithelium: proliferation and simple hyperplasia; proliferation inhibited by Na^{+}-ascorbic acid (750 mg/kg body weight and day), not by melatonin (75 mg/kg body weight and day) or N-acetylcysteine (0.4 mg/kg body weight and day)	Wei et al. 2005
rat, F344, 10 ♀	**10 weeks**, 0 or 100 mg **dimethylarsinic acid**/kg diet (Purina 5002) (about 0 or 7.5 mg dimethylarsinic acid/kg body weight and day), recovery period: 10 weeks	**about 7.5 mg/kg body weight**: normalization of food and water intake, bladder: persisting damage, relative weights ↑, hyperplasia, relative kidney weights ↑	Arnold et al. 1999
rat, F344, 3 ♂ and ♀	**13 weeks**, 0 or 184 mg **dimethylarsinic acid**/l drinking water (about 0 or 14 mg dimethylarsinic acid/kg body weight and day), purity: > 98%	**about 14 mg/kg body weight**: transitional epithelium of the bladder: cell changes, increased detachment and desquamation of epithelial cells, necrosis, particularly in ♀; only bladder examined by electron microscope; no effects on absolute and relative kidney and liver weights, blood parameters, activities of AST, ALT, AP and γ-GT, blood urea nitrogen	Shen et al. 2006

Table 4 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, F344, 10 ♂ and ♀	**13 weeks**, 0, 5, 50, 500, 2000 or 5000 mg **dimethylarsinic acid**/l drinking water (about 0, 0.38, 3.75, 37.5, 150 or 375 mg dimethylarsinic acid/kg body weight and day), purity: 99.5%	**about 0.38 mg/kg body weight**: NOAEL; ≥ **about 3.75 mg/kg body weight**: ♀: haemoglobin concentration ↓, erythrocyte count ↓, cholesterol and urea ↑, ♀: adrenal glands pale and relative weights ↓; **about 37.5 mg/kg body weight**: mortality 2 ♂/ 2 ♀; **about 37.5 mg/kg body weight and above**: hunched posture, emaciation, body weight gains ↓, haemoglobin concentration ↓, erythrocyte count ↓, reticulocyte count ↑, MCHC ↓, ♀: erythrocyte volume ↑, ♂: irritation in the gastrointestinal tract, relative weights of liver, kidneys and adrenal glands ↓; **about 150 mg/kg body weight and above**: all animals moribund or dead during the first weeks; symptoms of intoxication: motor activity ↓, wetness in the urogenital region, diarrhoea, discoloration around the nose, no grooming activity, serum: albumin ↓, ♂: activities of AST, ALT, γ-GT, CPK ↑; urine: quantity and dilution ↑, ♀: blood in urine; uterus and testes: size ↓	Luxembourg Industries 1987
rat, F344, 10 ♀	**20 weeks**, 0 or 100 mg **dimethylarsinic acid**/kg diet (Purina 5002) (about 0 or 7.5 mg dimethylarsinic acid/kg body weight and day)	**about 7.5 mg/kg body weight**: body weight gains ↑, water intake ↑, increase in some of the effects observed in kidneys and bladder after 10 weeks	Arnold et al. 1999

Table 4 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, F344, 60 ♂ and 60 ♀	**104 weeks**, 0, 2, 10, 40 or 100 mg **dimethylarsinic acid**/kg diet (author: 0, 0.18, 0.77, 3.1 or 7.8 mg dimethylarsinic acid/kg body weight and day), purity: 98.9%–100%	**0.18 mg/kg body weight**: ♀: relative adrenal weights ↑; **0.77 mg/kg body weight**: ♂: body weight gains transiently ↓, drinking water consumption ↑; **3.1 mg/kg body weight**: bladder: incidence of hyperplasia dose-dependently ↑, submucosa: lymphocytic infiltration (♂) and vacuolar degeneration of the urothelium (♀); kidneys: medullary calcinosis; **7.8 mg/kg body weight**: mortality (5 ♂), urine: volume ↑ and specific weight ↓, kidneys: hyperplasia of the epithelial lining of the papilla and pelvic urothelial cells, tubular cystic dilation in the medulla, papillary necrosis, thyroid gland: height of follicular epithelium ↑; bladder: incidence of papillomas and carcinomas ↑	Arnold et al. 2006
mouse, B6C3F1, 10 ♂ and 10 ♀	**15 weeks**, 0, 8, 40, 200 or 500 mg **dimethylarsinic acid**/kg diet (author: 0, 1.3, 7.8, 37 or 94 mg dimethylarsinic acid/kg body weight and day)	range-finding study to obtain dose levels for 2-year study (no other details)	Arnold et al. 2006
mouse, Ogg$^{-/-}$ (C57BI/6 J), 5 ♂ and 5 ♀	**72 weeks**, 0 or 200 mg **dimethylarsinic acid**/l drinking water (about 0 or 14 mg dimethylarsinic acid/kg body weight and day), purity: 99%	**about 14 mg/kg body weight**: relative weights of lungs, liver, spleen ↑, induction of genes specific to cell proliferation, cell signalling and xenobiotic metabolism, lungs: increased formation of microvilli and number of mitochondria; incidences of adenomas and adenocarcinomas (lungs) and of lymphomas and various types of leukaemia ↑ (see Section 5.7)	Kinoshita et al. 2007 a

Table 4 (continued)

Species, strain, number per group	Exposure	Findings	References
mouse, B6C3F1, 56 ♂ and 56 ♀	**104 weeks**, 0, 8, 40, 200 or 500 mg **dimethylarsinic acid**/kg diet (author: 0, 1.3, 7.8, 37 or 94 mg dimethylarsinic acid/kg body weight and day), purity: 98.9%–100%	**1.3 mg/kg body weight and above**: kidneys: progressive glomerulonephropathy, ♂: calcinosis; **7.8 mg/kg body weight and above**: bladder: ♀: dose-dependent vacuolization of the cells of the surface epithelium; **37 mg/kg body weight and above**: ♂: relative liver weights ↑, bladder: ♂: vacuolization of the cells of the surface epithelium; **94 mg/kg body weight**: ♂: body weight gains ↓, ♀: lymphocyte count ↓, monocyte count ↑, relative kidney weights ↑; ♂: increase in the incidence of skin fibrosarcomas not considered by the authors as substance-related	Arnold et al. 2006
dog, Beagle, 5 ♂ and 5 ♀	**52 weeks**, 0, 6.5, 16 or 40 mg **dimethylarsinic acid**/kg body weight and day, in gelatine capsules, 6 days/week, purity: 99.8%	**16 mg/kg body weight**: NOAEL; **40 mg/kg body weight**: diarrhoea, vomiting, salivation, plasma: albumin content ↓, ♂: liver weights ↑, soft intestinal contents	Luxembourg Industries 1989 a
sodium dimethylarsinate trihydrate			
rat, F344, 10 ♀	**4 weeks**, 0, 1, 4, 40 or 100 mg **sodium dimethylarsinate**/l drinking water (about 0, 0.15, 0.6, 6 or 15 mg/kg body weight and day), authors' conclusions were not included, as not reproducible, microscopic and transmission electron microscopic examination	**about 0.15 mg/kg body weight and above**: bladder: transitional epithelium: dose-dependent increase in cytoplasmic vacuolation and nuclear hyperchromatin; **about 0.6 mg/kg body weight and above**: number of mitochondria ↓, mitochondria swollen, with loss of cristae, vacuolation in superficial cells particularly pronounced; **about 15 mg/kg body weight**: transitional epithelium with necrosis and exfoliated cells, superficial cells changed in size, polymorphic microvilli and almost no recognizable mitochondria; no unusual findings with regard to body weights, body weight gains or food intake and in the expression of the DNA repair genes ERCC3/XPB, ATM, Polβ and XRCC1	Wang et al. 2009 b

Table 4 (continued)

Species, strain, number per group	Exposure	Findings	References
trimethylarsine oxide			
rat, F344, 25 ♂	**5, 10, 15 or 20 days**, 0 or 200 mg **trimethylarsine oxide**/kg diet (about 0 or 20 mg trimethylarsine oxide/kg body weight and day), purity: 99.9%	**about 20 mg/kg body weight**: total level of cytochrome P450 ↑ from day 10 onwards, relative liver weights ↑ from day 15 onwards, hydroxyl radicals in liver from day 10 onwards, liver: cell proliferation and apoptosis, induction of various Phase I and Phase II enzymes	Kinoshita et al. 2007 b
rat, F344, 3 ♂ and 3 ♀	**13 weeks**, 0 or 182 mg **trimethylarsine oxide**/l drinking water (about 0 or 14 mg trimethylarsine oxide/kg body weight and day), purity: > 98%	**about 14 mg/kg body weight**: body weight gains ↓; no effects on absolute and relative kidney and liver weights, blood parameters, activities of AST, ALT, AP and γ-GT, blood urea, bladder (only bladder examined by electron microscope)	Shen et al. 2006

AP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, ATM = ataxia telangiectasia mutant, CPK = creatine phosphokinase, ERCC3/XPB = excision repair cross-complementing group 3/xeroderma pigmentosum B, γ-GT = γ-glutamyl transferase, GST-P = placental form of glutathione S-transferase, MCHC = mean haemoglobin concentration per erythrocyte, 8-OHdG = 8-hydroxydesoxyguanosine, Polβ = DNA polymerase β, XRCC1 = X-ray repair cross-complementing group 1

In the gastrointestinal tract, inflammation, necrosis and perforated ulcerations of the mucosa were found. The adhesion of intestinal loops to each other or to neighbouring organs and peritonitis were observed. The inflammation observed in the ureter, bladder, kidneys, uterus, prostate gland, testes, epididymis and seminal vesicles was evaluated as a possible secondary effect of the perforated ulcers in the gastrointestinal tract (Arnold et al. 2003; Luxembourg Industries 1990).

In a 2-year study in mice, methylarsonic acid doses of 50 mg/kg body weight and day and above produced metaplasia in the caecum, colon and rectum, but no neoplasms. In the kidneys, nephropathy and calcification were found, and follicular hyperplasia was observed in the thyroid gland (Arnold et al. 2003).

Dimethylarsinic acid

In rats, intoxication symptoms were observed even after very low doses. The relative adrenal weight was increased after dimethylarsinic acid doses of about 0.18 mg/kg body weight and day and above (2-year study; Arnold et al. 2006). Initial changes in the kidneys after doses of about 0.15 mg/kg body weight and day and above consisted of an increase in the relative weight and calcification in the medulla–cortex transitional region (8-week study; Arnold et al. 1999). At dimethylarsinic acid doses of about 7.8 mg/kg body weight and day and above, hyperplasia of the epithelial lining of the papillae and pelvic urothelial cells, cystic dilation of the medullary tubules and papillary necrosis were described (2-year study; Arnold et al. 2006). In the bladder, at about 1.5 mg dimethylarsinic acid/kg body weight and day and above there was a dose-dependent increase in cell proliferation in the surface epithelium (8-week study; Wanibuchi et al. 1996), at about 3.1 mg dimethylarsinic acid/kg body weight and day and above there was a dose-dependent increase in the incidence of hyperplasia and submucosal lymphocytic infiltration, and vacuolar degeneration of the urothelium (2-year study; Arnold et al. 2006). At dimethylarsinic acid doses of about 3 mg/kg body weight and day and above (10-week study; Arnold et al. 1999) the relative weight was increased, and at about 7.8 mg/kg body weight and day and above in a 2-year study the incidence of papillomas and carcinomas of the bladder (see Section 5.7) was increased (Arnold et al. 2006). In the liver, necrosis occurred and fatty degeneration of the surface epithelium of the hepatocytes located around the central vein was found (8-week study; Wanibuchi et al. 1996). For sodium dimethylarsinate trihydrate, a lowest observed adverse effect level (LOAEL) of 0.15 mg/kg body weight and day was determined in rats based on an increase in vacuole formation in the cytoplasm and the presence of hyperchromatin in the nucleus of transitional epithelial cells detected by means of electron microscopic examination of the bladder (Wang et al. 2009 b).

Mice were less sensitive to dimethylarsinic acid than rats, although the damage was nevertheless found to be similar (Arnold et al. 2006).

Summary:

After oral administration of methylarsonic acid, the LOAEL for hyperplasia of the bladder was about 2 mg/kg body weight and day in rats. For dimethylarsinic acid, a LOAEL of about 0.2 mg/kg body weight and day was obtained in rats for the increase in relative kidney weights and of 0.3 mg/kg body weight and day for calcifications in the corticomedullary region of the kidney. For sodium dimethylarsinate

Table 5 Effects of methylarsenic compounds after repeated dermal application

Species, strain, number per group	Exposure	Findings	References
methylarsonic acid			
rabbit, New Zealand White 5 ♂ and 5 ♀	**21 days**, 0, 100, 300 or 1000 mg **methylarsonic acid**/kg body weight and day, occlusive, 6 hours/day, 5 days/week, purity: 99.95%	**100 mg/kg body weight**: NOAEL; **300 mg/kg body weight and above**: ♂: dose-dependent decrease in the cholesterol level in the blood	Luxembourg Industries 1991 b
dimethylarsinic acid			
rabbit, New Zealand White, 5 ♂ and 5 ♀	**21 days**, 0, 100, 300 or 1000 mg **dimethylarsinic acid**/kg body weight and day, occlusive, 6 hours/day, 5 days/week, purity: 99.95%	**300 mg/kg body weight**: NOAEL, hypospermia 1/5; **1000 mg/kg body weight**: ♀: relative and absolute adrenal weights ↓, ♂: hypospermia in 4/5; no irritation	Luxembourg Industries 1991 a

trihydrate, a LOAEL of 0.15 mg/kg body weight and day was determined in rats for degenerative changes in the cells of the transitional epithelium of the bladder.

5.2.3 Dermal application

In the 3-week studies with dermal application of **methylarsonic acid** or **dimethylarsinic acid** (see Table 5), no local effects were found in rabbits up to 1000 mg/kg body weight and day for either substance (Luxembourg Industries 1991 a, b). At doses of 300 mg/kg body weight and day and above, **methylarsonic acid** reduced the cholesterol level in the males in a dose-dependent manner (Luxembourg Industries 1991 b), which was found also in rats after oral administration (Arnold et al. 2003; Luxembourg Industries 1990). The hypospermia occurring in male rabbits at 1000 mg **dimethylarsinic acid**/kg body weight and day was attributed by the authors to delayed spermatogenesis and immaturity of the animals (Luxembourg Industries 1991 a). Even though hypospermia was not observed in rats after oral administration, a substance-related effect cannot be excluded.

Dimethylarsinic acid doses of 0, 1 or 10 mg/kg body weight were applied to the dorsal skin of female BALB/c mice once a week for 4 weeks. The females were mated with untreated males after the first application. Skin thickness and the expression of the apoptosis-related factors Bcl-2, Bcl-3, Bad and Bid, and caspase-3, 6, 8, 9 and 12 in the skin were examined during pregnancy and one day after birth. In the dams, at dose levels of 1 mg/kg body weight and day and above, treatment with dimethylarsinic acid led to increased skin thickness and the increased expression of

Bcl-2, Bad and caspase-12 at the mRNA and protein level (see Section 5.5.2) (Kim et al. 2012).

Summary:

After dermal application of methylarsonic acid or dimethylarsinic acid, no local effects occurred in rabbits up to 1000 mg/kg body weight and day. The no observed adverse effect levels (NOAELs) for methylarsonic acid and dimethylarsinic acid were 100 and 300 mg/kg body weight, respectively, in rabbits after 3 weeks of exposure. In the skin of mice, 4-week dermal application of dimethylarsinic acid doses of 1 mg/kg body weight and day and above resulted in increased skin thickness and the increased expression of genes participating in apoptosis and of caspase-12.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

After whole-body exposure to **dimethylarsinic acid** concentrations of up to 6940 mg/m^3, only female Sherman rats developed erythema on the paws and ears with a reddish discoloration of the fur. These changes, which did not occur in male rats or Swiss Webster mice, were attributed to irritation caused by direct contact with dust (Stevens et al. 1979).

In 21-day dermal studies in rabbits, **methylarsonic acid** and **dimethylarsinic acid** were not found to be irritating to the skin up to 1000 mg/kg body weight and day (Luxembourg Industries 1991 a, b).

Sodium methylarsonate had a slight irritating effect on the intact skin of rabbits (Jaghabir et al. 1988).

5.3.2 Eyes

In 6 New Zealand White rabbits, the instillation of **sodium methylarsonate** into the conjunctival sac caused reddening and swelling of the conjunctiva and lacrimation. Five rabbits recovered after 96 hours and one after 120 hours (US EPA 2006).

5.4 Allergenic effects

There are no data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

The results of the available fertility studies are shown in Table 6.

In a 2-generation feeding study in rats, after **methylarsonic acid** doses of 76 mg/kg body weight and day, the body weight gains were delayed by 8.6% and 9.3% in the male parents of the F0 and F1 generations, respectively, and the fertility index was decreased.

Table 6 Effects of methylarsenic compounds on fertility

Species, strain, number per group	Exposure	Findings	References
methylarsonic acid			
rat, CD, 30 ♂ and 30 ♀	**2-generation study**, 0, 100, 300 or 1000 mg **methylarsonic acid**/kg diet (before mating: 0, 7, 22 or 76 mg methylarsonic acid/kg body weight and day, during lactation: 0, 7.4, 23.1 or 83.2 mg methylarsonic acid/kg body weight and day), F0 and F1: 14 days before, 21 days during mating, ♀ up to weaning on day 21 after birth	**7 mg/kg body weight**: parents: ♂: NOAEL; **22 mg/kg body weight**: parents: ♂: F0 body weight gains ↓, not in F1; foetuses and offspring: NOAEL; **76 mg/kg body weight**: parents: ♂: F0 + F1: body weight gains 8.6% and 9.3% ↓, F0 + F1: pregnancy index ↓, ♂: fertility index ↓; offspring: day 4–21 after birth: surviving animals ↓; no unusual findings in gross-pathological and microscopic examinations of testes, epididymis, seminal vesicles or sperms (number, morphology, motility) or gross-pathological examination of F1 and F2 offspring	Luxembourg Industries 1994 b
sodium methylarsonate			
mouse, Swiss, 10 ♂ and 10 ♀	**10 weeks**, 0, 11.9 or 119 mg **sodium methylarsonate**/kg body weight and day, gavage, 3 days/week only ♂, mating 1:1	**controls**: 100% ♀ with offspring; **11.9 mg/kg body weight and above**: body weight gains ↓, 50% ♀ with offspring; **119 mg/kg body weight**: no ♀ with offspring; no unusual findings for erythrocyte and leukocyte count, haematocrit value or total protein in the serum	Prukop and Savage 1986
mouse, Swiss, 10 ♂ treated, 10 ♀ untreated	**10 weeks**, 0 or 119 mg **sodium methylarsonate**/kg body weight and day, gavage, 3 days/week, mating 1:1	**controls**: 90% ♀ with offspring; **119 mg/kg body weight**: 50% ♀ with offspring, ♀: maternal instincts (nest making, care of offspring) ↓; not significantly changed: litter size and litter weights, body weights of offspring at birth and after 3 weeks	Prukop and Savage 1986

Table 6 (continued)

Species, strain, number per group	Exposure	Findings	References
rabbit, New Zealand White, 2 ♀	**12 weeks**, 0 or 50 mg **sodium methylarsonate**/kg diet (about 0 or 1.5 mg sodium methylarsonate/kg body weight and day), examined on days 1 and 20 after birth	**1.5 mg/kg body weight**: offspring on days 1 and 20 after birth: no unusual findings (no other details)	Exon and Harr 1974
dimethylarsinic acid			
rat, CD, 25 ♂ and 25 ♀	**2-generation study**, 0, 3, 21 or 147 mg **dimethylarsinic acid**/kg diet (♂: 0, 0.3, 1.8 or 12.9 mg dimethylarsinic acid/kg body weight and day, ♀: 0, 0.3, 2.2 or 14.9 mg dimethylarsinic acid/kg body weight and day)	**0.3 mg/kg body weight and above**: ♀: drinking water intake transiently ↓; **1.8/2.2 mg/kg body weight**: F2: 1 dead animal without sacral vertebrae 2, 3 and 4; **12.9/14.9 mg/kg body weight**: F0: ♂: drinking water intake transiently ↑; ♀: MCV ↑, erythrocyte count ↓ (F1 and F2 not examined); F1: ♀: absolute and relative ovary weights ↓, ♀: thyroid: transformation of follicular epithelium from cubic into columnar shape; 1 stillborn pup (brachygnathia, shortened skull bones, angular deformation of ribs and bones in the thoracic and pelvic regions), 1 foetus with diaphragmatic hernia; F2: mortality: 1 dam (haemorrhagic gastric content, punctiform haemorrhage in thymus), 1 stillborn pup (small skull bone and scoliosis); no substance-related unusual findings on oestrous cycle, fertility index, gestation index, growth and development of offspring	Luxembourg Industries 1989 b

Table 6 (continued)

Species, strain, number per group	Exposure	Findings	References
rabbit, New Zealand White, 5 ♂ and 5 ♀	**21 days**, 0, 100, 300 or 1000 mg **dimethylarsinic acid**/kg body weight and day, dermal (occlusive), 6 hours/day, 5 days/week, purity: 99.95%	**300 mg/kg body weight**: NOAEL, ♂: hypospermia 1/5; **1000 mg/kg body weight**: ♀: relative and absolute adrenal weights ↓, ♂: hypospermia in 4/5; authors: hypospermia is evidence of delayed maturity of the animals; no irritation	Luxembourg Industries 1991 a

MCV = mean erythrocyte volume

In addition, the gestation index and number of pups surviving up to day 21 after birth were decreased (Luxembourg Industries 1994 b). For the foetuses and offspring, a NOAEL of 22 mg methylarsonic acid/kg body weight and day was obtained in this study. As in the offspring the additional uptake of methylarsonic acid via the mother's milk and food occurred, it is not possible to ascertain whether a postnatal effect might have been involved.

After male mice were treated for 10 weeks with **sodium methylarsonate** doses of 11.9 mg/kg body weight and day and above and subsequently mated, only half of the untreated females had offspring (Prukop and Savage 1986). The LOAEL for fertility was therefore 11.9 mg sodium methylarsonate/kg body weight and day.

In a 2-generation feeding study, changes in the erythrocyte count and erythrocyte volume, reduced relative ovarian weights and a change in the follicular epithelium of the thyroid gland were observed in the female animals at 14.9 mg **dimethylarsinic acid**/kg body weight and day. In the foetuses, no unusual substance-related findings in growth and development were found (Luxembourg Industries 1989 b). The NOAEL for foetotoxicity is therefore 14.9 mg dimethylarsinic acid/kg body weight and day.

In male rabbits, the dermal application of 1000 mg **dimethylarsinic acid**/kg body weight produced hypospermia; this was attributed to delayed spermatogenesis or delayed maturity of the animals (Luxembourg Industries 1991 a).

Summary:

From the available studies, a NOAEL for fertility of 22 mg **methylarsonic acid**/kg body weight and day was obtained for rats and a LOAEL of 11.9 mg **sodium methylarsonate**/kg body weight for mice. In rats, a NOAEL of 14.9 mg **dimethylarsinic acid**/kg body weight and day was obtained for fertility and foetotoxicity.

5.5.2 Developmental toxicity

The studies of developmental toxicity are presented in detail in Table 7.

In rats, the NOAEL for maternal toxicity and reduced foetal weights was 100 mg **methylarsonic acid**/kg body weight and day. No teratogenic effects were found (Irvine et al. 2006). In rabbits, the NOAEL was 12 mg methylarsonic acid/kg body weight and day for skeletal variations (Irvine et al. 2006).

Dimethylarsinic acid was found to have the highest developmental toxicity among the methylarsenic compounds. In rats, pre-implantation losses occurred at 12 mg dimethylarsinic acid/kg body weight and day, and post-implantation losses at doses of 36 mg/kg body weight and day and above. In the foetuses, delayed ossification, skeletal variations and reduced body weights were found at 36 mg/kg body weight and day and above (Irvine et al. 2006). In rats, the NOAEL was therefore 4 mg dimethylarsinic acid/kg body weight and day for pre-implantation losses and 12 mg dimethylarsinic acid/kg body weight and day for developmental toxicity. From a 2-generation study, a NOAEL for foetotoxicity of 14.9 mg dimethylarsinic acid/kg body weight and day was derived for rats (see Section 5.5.1 and Table 6). In rabbits, a NOAEL of 12 mg dimethylarsinic acid/kg body weight and day for maternal and developmental toxicity was obtained (Irvine et al. 2006).

Table 7 Studies of the toxic effects on prenatal development of methylarsenic compounds

Species, strain, number per group	Exposure	Findings	References
methylarsonic acid			
rat, Sprague Dawley, 25 ♀	**GD 6–15**, 0, 10, 100 or 500 mg **methylarsonic acid**/kg body weight and day, gavage, examination on GD 20	≥ **10 mg/kg body weight**: dams: body weight gains ↓; **100 mg/kg body weight**: foetuses: NOAEL; **500 mg/kg body weight**: dams: stained fur in the anogenital area, soft faeces, 1 animal died prematurely; foetuses: weights ↓, no teratogenic effects	Irvine et al. 2006
rabbit, New Zealand White, 14 ♀	**GD 7–19**, 0, 1, 3, 7 or 12 mg **methylarsonic acid**/kg body weight and day, gavage, examination on GD 29	**7 mg/kg body weight**: dams: and foetuses: NOAEL; **12 mg/kg body weight**: dams: food intake ↓, body weight gains ↓, abortion in 2/13 animals, soft faeces or diarrhoea; foetuses: skeletal variations: 13 pairs of sternal ribs, 8 lumbar vertebrae	Irvine et al. 2006
hamster, no other details	**GD 8**, 0, 20, 50 or 100 mg **methylarsonic acid**/kg body weight, i. v., examination on GD 14	**100 mg/kg body weight**: NOAEL; due to the route of administration, the study is not included in the evaluation	Willhite 1981

Table 7 (continued)

Species, strain, number per group	Exposure	Findings	References
disodium methylarsonate			
mouse, CD1, no other details	**GD 8, 9 or 10–15**, 0 or 15 000 mg **disodium methylarsonate**/kg body weight, i. p., examination on GD 18	**15 000 mg/kg body weight:** **treatment GD 8**: foetuses: gross-pathological examination: 1.5% malformations; **treatment GD 9**: foetuses: gross-pathological examination: 3.7% malformations: 31% fused ribs, death and resorptions 37% (no other details); **treatment GD 10–15**: foetuses: gross-pathological examination: 1.0% malformations, 28% fused ribs, death and resorptions 43% (no other details), body weights decreased by about 15%; due to the route of administration, the study is not included in the evaluation	Harrison et al. 1980
mouse, CD1, no other details	**GD 11, 12, 13 or 14,** 0 or 1200 mg **disodium methylarsonate**/kg body weight, i. p., examination on GD 18	**treatment GD 11 or 14**: **1200 mg/kg body weight**: foetuses: no unusual findings with regard to number of dead or resorbed foetuses; **treatment GD 12 or 13**: **1200 mg/kg body weight**: foetuses: number of dead or resorbed foetuses increased in a time-dependent manner, foetal weights ↓; no examination for malformations; due to the route of administration, the study is not included in the evaluation	Hood 1998

Table 7 (continued)

Species, strain, number per group	Exposure	Findings	References
mouse, CD1, no other details	**GD 8, 9, 10 or 11** 0 or 1500 mg **disodium methylarsonate**/kg body weight, i. p., examination on GD 18	**1500 mg/kg body weight**: dams: mortality; foetuses: number of dead or resorbed foetuses ↑, foetal weights ↓, skeletal malformations ↑; due to the route of administration, the study is not included in the evaluation	Hood 1998
hamster, 10 ♀	**GD 8, 9, 10, 11 or 12**, 0 or 500 mg **disodium methylarsonate**/kg body weight, i. p., examination on GD 15	**500 mg/kg body weight**: dams: mortality; foetuses: exencephaly, lip-palate cleft, short muzzle or fused ribs (on GD 9, 10 or 12); due to the route of administration, the study is not included in the evaluation	Hood et al. 1982
dimethylarsinic acid			
rat, Sprague Dawley, 22 ♀	**GD 6–15**, 0, 4, 12 or 36 mg **dimethylarsinic acid**/kg body weight and day, gavage, examination on GD 20	**4 mg/kg body weight**: dams: NOAEL; **12 mg/kg body weight**: dams: pre-implantation losses ↑; foetuses: NOAEL; **36 mg/kg body weight**: dams: food intake ↓, body weight gains ↓, number of corpora lutea ↓, placental weights ↓; foetuses: post-implantation losses ↑, body weights ↓, incidence of pleural hernia ↑, skeletal variations: delayed ossification of skull, sternum, thoracic vertebrae and metacarpal bones, short or rudimentary 13th ribs	Irvine et al. 2006

Table 7 (continued)

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 25 ♀	**GD 6–15**, 0 or 40 mg **dimethylarsinic acid**/kg body weight and day, gavage, examination on GD 20	**40 mg/kg body weight**: dams: NOAEL; foetuses: body weights ↓, thymus weights ↓	Chernoff et al. 1990
rat, CD, 21 ♀	**GD 7–16**, 0, 7.5, 15, 30, 40, 50 or 60 mg **dimethylarsinic acid**/kg body weight and day, gavage, examination on GD 20	**7.5 mg/kg body weight and above**: dams: gestation rate ↓; **30 mg/kg body weight and above**: foetuses: irregular palatine folds (evaluation of findings not clear); **40 mg/kg body weight and above**: dams: dose-dependent increase in mortality, body weight gains ↓; foetuses: body weights ↓, delayed ossification of sternum and tail bones, fused vertebrae and ribs, shortened tails, additional ribs; **50 mg/kg body weight and above**: foetuses: mortality ↑; **60 mg/kg body weight**: dams: mortality 67%	Rogers et al. 1981
mouse, CD1, 30–32 ♀	**GD 7–16**, 0, 200, 400 or 600 mg **dimethylarsinic acid**/kg body weight and day, gavage, examination on GD 18	**200 mg/kg body weight and above**: dams: body weight gains ↓; **400 mg/kg body weight and above**: dams: dose-dependent increase in mortality; foetuses: dose-dependent increase in mortality, dose-dependent decrease in body weights, delayed ossification of tail bones, additional ribs	Rogers et al. 1981
mouse, CD1, 19–40 ♀	**GD 8**, 0, 1600 or 2400 mg **dimethylarsinic acid**/kg body weight, gavage, examination on GD 18	**1600 mg/kg body weight and above**: dams: mortality, body weight gains ↓, total resorptions; foetuses: body weights ↓, delayed ossification of sternum and tail bones, enlarged cerebral ventricles, additional ribs; **2400 mg/kg body weight**: foetuses: enlarged renal pelvis	Kavlock et al. 1985

Table 7 (continued)

Species, strain, number per group	Exposure	Findings	References
rabbit, New Zealand White, 15 ♀	**GD 7–19**, 0, 3, 12 or 48 mg **dimethylarsinic acid**/kg body weight and day, gavage, examination on GD 29	**12 mg/kg body weight**: dams and foetuses: NOAEL; **48 mg/kg body weight**: dams: food intake ↓, body weight gains ↓, abortions ↑, little or no faeces or diarrhoea, fluids in the gastrointestinal tract, haemorrhages in the stomach; foetuses: no survivors	Irvine et al. 2006
hamster, no other details	**GD 8**, 0, 20, 50 or 100 mg **dimethylarsinic acid**/kg body weight, i. v., examination on GD 14	**100 mg/kg body weight**: NOAEL; due to the route of administration, the study is not included in the evaluation	Willhite 1981
sodium dimethylarsinate			
mouse, CD1, no other details	**GD 11, 12, 13 or 14**, 0 or 800 mg **sodium dimethylarsinate**/kg body weight, i. p., examination on GD 18	**treatment GD 11 or 12**: **800 mg/kg body weight**: foetuses: no unusual findings with regard to the number of dead or resorbed foetuses or body weights; **treatment GD 13 or 14**: **800 mg/kg body weight**: foetuses: number of dead or resorbed foetuses ↑, weights unchanged; no examination for malformations; due to the route of administration, the study is not included in the evaluation	Hood 1998

Table 7 (continued)

Species, strain, number per group	Exposure	Findings	References
mouse, CD1, no other details	**GD 8, 9 or 10**, 0 or 1200 mg **sodium dimethylarsinate**/kg body weight, i. p., examination on GD 18	**treatment GD 8 or 10**: **1200 mg/kg body weight**: foetuses: no significant findings in number of dead or resorbed foetuses, skeletal malformations ↑ (GD 8); **treatment GD 9**: **1200 mg/kg body weight**: dams: mortality; foetuses: time-dependent increase in number of dead or resorbed foetuses, skeletal malformations ↑; due to the route of administration, the study is not included in the evaluation	Hood 1998
hamster, 10 ♀	**GD 8, 9, 10, 11 or 12**, 0 or 900 mg **sodium dimethylarsinate**/kg body weight, i. p., examination on GD 15	**900 mg/kg body weight**: dams: mortality GD 8 (83%), GD 9 (95%), GD 10 and 11 (about 55%), GD 12 (29%); foetuses: stunted with exencephaly, cleft palate, lips and jaws, syndactyly or club feet (in particular GD 9 and 10); due to the route of administration, the study is not included in the evaluation	Hood et al. 1982
hamster, 10 ♀	**GD 8, 9, 10, 11 or 12**, 0 or 1000 mg **sodium dimethylarsinate**/kg body weight, i. p., examination on GD 15	**1000 mg/kg body weight**: dams: 100% mortality on GD 8, 9 and 12; foetuses: 100% mortality an GD 8, 9 and 12; due to the route of administration, the study is not included in the evaluation	Hood et al. 1982

GD qestation day; i.v. intravenous; i.p. intraperitoneal

Dimethylarsinic acid was applied to the dorsal skin of female BALB/c mice in doses of 0, 1 or 10 mg/kg body weight once a week for 4 weeks. After the first application, the females were mated with untreated males. Skin thickness and the expression of the apoptosis-related factors Bcl-2, Bcl-3 Bad and Bid, and caspase-3, 6, 8, 9 and 12 in the skin were examined during pregnancy in the dams and also one day after birth in both dams and foetuses. Treatment with dimethylarsinic acid increased the skin thickness and the expression of Bcl-2, Bad and caspase-12 at the mRNA and protein level in the dams, but not in the offspring (Kim et al. 2012).

Summary:

As regards the developmental toxicity of methylarsenic compounds, rats and rabbits are considerably more sensitive than mice. Oral administration of methylarsonic acid to pregnant rabbits produced skeletal variations in the foetuses at 12 mg/kg body weight. In rats, pre-implantation losses occurred at dimethylarsinic acid doses of 12 mg/kg body weight and post-implantation losses, skeletal variations and delayed ossification in the foetuses at doses of 36 mg/kg body weight and above. In rabbits, all foetuses died after dimethylarsinic acid doses of 48 mg/kg body weight. In mice, in addition to increased mortality in the dams and foetuses at dose levels of 400 mg dimethylarsinic acid/kg body weight and above, delayed ossification and skeletal variations were found in the foetuses.

5.6 Genotoxicity

5.6.1 In vitro

Mutagenicity tests with Salmonella typhimurium yielded negative results for methylarsenic compounds. Chromosomal aberrations, oxidation of DNA, impairment of DNA repair processes, DNA strand breaks, micronuclei and other clastogenic effects in the µM range are caused by various methylarsenic compounds (see Table 8). Only **methylarsonous acid** led to sister chromatid exchange in mammalian cells. In V79 cells, 10 mM **dimethylarsinic acid** inhibited the correct synthesis of centrosomes and their kinesin-dependent migration to the cell poles on the opposite side (Ochi 2000, 2002; Ochi et al. 1999). This also explains the mitotic arrest in human lymphocytes (Kligerman et al. 2003, 2005), V79 cells (Eguchi et al. 1997) or A431 cells (Naranmandura et al. 2007 a) caused by **methylarsonic acid**, **dimethylarsinous acid**, **dimethylarsinic acid**, **dimethylthioarsinic acid** and **trimethylarsine oxide**. Hypoploidy or hyperploidy in MRC-5 cells were induced at 12.5 µM **dimethylarsinic acid** and above (Güerci et al. 2000). **Dimethylarsinic acid** and **trimethylarsine oxide**, but not **methylarsonic acid**, caused tetraploids in V79 cells (Eguchi et al. 1997).

The unidentified metabolites (see Section 3.1 and Section 3.2) occurring in rats after the administration of **dimethylarsinic acid** with the drinking water are possibly also genotoxic. It was possible to identify two of these metabolites in a solution with **dimethylarsinic acid** (1 mM), Escherichia coli A3-6 and various cysteine concentrations (1–7 mM); cysteine was necessary for the formation of the metabolites by Escherichia coli A3-6. When V79 cells were cultured for 6 hours in a solution of **dimethylarsinic acid**, Escherichia coli A3-6 and cysteine, there was a significant increase in C-mitosis, tetraploidy, mitotic arrest, sister chromatid exchange and chromosomal aberrations depending on the cysteine concentration.

Table 8 The genotoxicity of methylarsenic compounds in vitro

End point	Substance	Test system	Concentration	Effective concentration[a)]	Cytotoxicity[a)]	Results	References
gene mutation, bacteria	methylarsonous acid	Salmonella typhimurium TA98, TA100, TA104	0.05–94.3 µM	–	23.5 µM and above	–	Kligerman et al. 2003
	methylarsonic acid		1.54–15 432 µM	–	–	–	
	dimethylarsinous acid		0.43–2155 µM	–	431 µM and above	–	
	dimethylarsinic acid		1.56–15 625 µM	–	–	–	
SCE	methylarsonous acid	human lymphocytes	0.1–2.7 µM	–	1.8 µM and above	–	Kligerman et al. 2003
		CHO cells	100 µM	100 µM	–	+	Dopp et al. 2004
	methylarsonic acid	human lymphocytes	10–10 000 µM	–	10 000 µM	–	Kligerman et al. 2003
		CHO cells	10 000 µM	–	500 µM	–	Dopp et al. 2004
	dimethylarsinous acid	human lymphocytes	0.11–12.26 µM	1.35 µM	2.7 µM	(+)	Kligerman et al. 2003
		CHO cells	50 µM	50 µM	10 µM	–	Dopp et al. 2004
	dimethylarsinic acid	human lymphocytes	10–10 000 µM	1000 µM	10 000 µM	–	Kligerman et al. 2003
		CHO cells	10 000 µM	–	500 µM	–	Dopp et al. 2004
		lymphoblastoid cells	0.1–10 µM	–	5 µM	–	Rasmussen and Menzel 1997
	dimethylthioarsinic acid	SHE cells	10–50 µM	20 µM	50 µM	+	Ochi et al. 2008
	trimethylarsine oxide	CHO cells	10 000 µM	–	500 µM	–	Dopp et al. 2004

Table 8 (continued)

End point	Substance	Test system	Concentration	Effective concentration[a)]	Cytotoxicity[a)]	Results	References
DNA repair inhibition	methylarsonous acid	A549 cells	2.5–7.5 µM	2.5 µM and above	–	+	Schwerdtle et al. 2003 b
		HeLa-S3 cells	0.1 µM	0.1 µM	–	+	Walter et al. 2007
	methylarsonic acid	A549 cells	250–500 µM	250 µM and above	–	+	Schwerdtle et al. 2003 b
		HeLa-S3 cells	100 µM	100 µM	–	+	Walter et al. 2007
	dimethylarsinous acid	A549 cells	2.5–7.5 µM	2.5 µM and above	–	+	Schwerdtle et al. 2003 b
		HeLa-S3 cells	0.1 µM	0.1 µM	–	+	Walter et al. 2007
	dimethylarsinic acid	A549 cells	250–500 µM	250 µM and above	–	+	Schwerdtle et al. 2003 b
		HeLa-S3 cells	100 µM	100 µM	–	+	Walter et al. 2007
		primary bladder cells from rats pretreated with dimethylarsinic acid + H_2O_2 or formaldehyde	–	–	–	–	Wang et al. 2009 a
DNA oxidation alkaline unwinding + fpg-protein	methylarsonous acid	HeLa cells	0.1–7.5 µM	0.1 µM and above	7.5 µM	+	Schwerdtle et al. 2003 a
	methylarsonic acid		10–500 µM	10 µM and above	–	+	Schwerdtle et al. 2003 a
	dimethylarsinous acid		0.1–7.5 µM	0.1 µM and above	7.5 µM	+	Schwerdtle et al. 2003 a
	dimethylarsinic acid		10–500 µM	10 µM and above	–	+	Schwerdtle et al. 2003 a

Table 8 (continued)

End point	Substance	Test system	Concentration	Effective concentration[a)]	Cytotoxicity[a)]	Results	References
DNA breaks comet assay	methylarsonous acid	human lymphocytes	10 000–30 000 µM	30 000 µM	no data	+	Mass et al. 2001
		HL60 cells	0.1–1.0 µM	0.1 µM and above	–	+	Wang et al. 2002
		primary human hepatocytes	0.1–5.0 µM	5 µM	20 µM and above	+	Dopp et al. 2008
	methylarsonic acid	HL60 cells	0.1–1.0 µM	1 µM and above	–	+	Wang et al. 2002
	dimethylarsinous acid	primary human hepatocytes	10–500 µM	–	13 µM	–	Dopp et al. 2008
		human lymphocytes	40–1000 µM	150 µM	no data	+	Mass et al. 2001
	dimethylarsinic acid	HL60 cells	0.1–1.0 µM	1 µM and above	–	+	Wang et al. 2002
		human lymphocytes	100-300 000 µM	–	no data	–	Mass et al. 2001
DNA breaks alkaline unwinding	methylarsonous acid	HeLa cells	0.1–7.5 µM	0.1 µM and above	7.5 µM	+	Schwerdtle et al. 2003 a
	methylarsonic acid		10–500 µM	–	–	–	Schwerdtle et al. 2003 a
	dimethylarsinous acid		0.1–7.5 µM	2.5 µM and above	–	+	Schwerdtle et al. 2003 a
		human alveolar cells (L-132)				+	Yamanaka et al. 1990

Table 8 (continued)

End point	Substance	Test system	Concentration	Effective concentration[a)]	Cytotoxicity[a)]	Results	References
		primary mouse lung cells	100–500 µM	100 µM and above	no data	+	Yamanaka et al. 1989
	dimethylarsinic acid	primary mouse lung cells	100–500 µM	–	no data	–	Yamanaka et al. 1989
		human alveolar cells (L-132)	10 000 µM		no data	+	Kawaguchi et al. 1996; Rin et al. 1995; Tezuka et al. 1993
	dimethylthioarsinic acid	A549 cells	0.01–100 µM	–	–	–	Bartel et al. 2011
		human urothelial cells	0.5–5 µM	5 µM	5 µM	+	Ebert et al. 2013
SCGE Assay	methylarsonic acid	human lymphocytes	0.5–50 µM	0.5 µM and above	–	+	Sordo et al. 2001
		human leukocytes	0.5–50 µM	from 0.5 µM	–	+	Sordo et al. 2001
		primary mouse spleen lymphocytes	2.5–10 µM	from 2.5 µM	–	+	Tennant and Kligerman 2011
	dimethylarsinic acid	human lymphocytes	1.0–5.0 µM	from 1.0 µM	–	+	Sordo et al. 2001
		human leukocytes	0.5–50 µM	0.5 µM and above	–	+	Sordo et al. 2001
		primary mouse spleen lymphocytes	2.5–10 µM	2.5 µM and above	–	+	Tennant and Kligerman 2011
spindle disturbances	dimethylthioarsinic acid	SHE cells	10–200 µM	20 µM and above	50 µM	+	Ochi et al. 2008

Table 8 (continued)

End point	Substance	Test system	Concentration	Effective concentration[a)]	Cytotoxicity[a)]	Results	References
SS breaks and DNA protein crosslinks	dimethylarsinic acid	human alveolar cells (L-132)	10 000 µM	10 000 µM after 8–9 hours incubation and above	no data	+	Kato et al. 1994; Yamanaka et al. 1993, 1995
CA	methylarsonous acid	CHO cells	10–100 µM	10 µM and above	–	+	Dopp et al. 2004
		primary mouse spleen lymphocytes	3–5 µM	3 µM and above	–	+	Kligerman et al. 2010
	methylarsonic acid	CHO cells	10–10 000 µM	–	–	–	Dopp et al. 2004
		human umbilical cord fibroblasts	1400–21 400 µM	1400 µM	no data	+	Oya-Ohta et al. 1996
	dimethylarsinous acid	CHO cells	50–100 µM	50 µM and above	–	+	Dopp et al. 2004
	dimethylarsinic acid	human umbilical cord fibroblasts	700–7200 µM	700 µM	no data	+	Oya-Ohta et al. 1996
		CHO cells	100–10 000 µM	–	–	–	Dopp et al. 2004
	dimethylthioarsinic acid	SHE cells	10–50 µM	20 µM	50 µM	+	Ochi et al. 2008
	trimethylarsine oxide	human umbilical cord fibroblasts	3700–14 700 µM	3700 µM	no data	+	Oya-Ohta et al. 1996
		CHO cells	10–10 000 µM	–	–	–	Dopp et al. 2004
	tetramethylarsonium iodide	human umbilical cord fibroblasts	4000–38 000 µM	1900 µM	no data	+	Oya-Ohta et al. 1996

Table 8 (continued)

End point	Substance	Test system	Concentration	Effective concentration[a)]	Cytotoxicity[a)]	Results	References
micronuclei	methylarsonous acid	fibroblasts (CHO-9)	2.5–7.5 µM	5 µM and above	100 µM	+	Dopp et al. 2004, 2005
		human lymphocytes	0.01–2 µM	2 µM	–	+	Colognato et al. 2007
		A549 cells	0.1–5 µM	0.5 µM and above	–	+	Bartel et al. 2011
	methylarsonic acid	fibroblasts (CHO-9)	2.5–7000 µM	–	–	–	Dopp et al. 2005
		human lymphocytes	50–1000 µM	500 µM	750 µM and above	+	Colognato et al. 2007
		A549 cells	100–500 µM	250 µM	–	+	Bartel et al. 2011
	dimethylarsinous acid	fibroblasts (CHO-9)	0.1–10 µM	1 µM and above	10 µM	+	Dopp et al. 2004, 2005
		A549 cells	0.1–5 µM	2 µM[a)]	5 µM	+	Bartel et al. 2011
	dimethylarsinic acid	fibroblasts (CHO-9)	0.1–1000 µM	–	–	–	Dopp et al. 2005
		human lymphocytes	50–750 µM	–	500 µM and above	–	Colognato et al. 2007
		A549 cells	100–500 µM	250 µM	–	+	Bartel et al. 2011
	dimethylthioarsinic acid	A549 cells	5–20 µM	5 µM[a)]	30 µM	+	Bartel et al. 2011
	trimethylarsine oxide	fibroblasts (CHO-9)	5–5000 µM	–	–	–	Dopp et al. 2005
		human lymphocytes	100–1000 µM	–	–	–	Colognato et al. 2007
gene mutation							
$TK^{+/-}$, small colonies	methylarsonous acid	L5178Y mouse lymphoma cells	0.19–0.57 µM	0.38 µM	0.47 µM	+	Kligerman et al. 2003
	methylarsonic acid	L5178Y mouse lymphoma cells	2000–5000 µg/ml	2500 µg/ml and above	3000 µg/ml and above	+	Moore et al. 1997

Table 8 (continued)

End point	Substance	Test system	Concentration	Effective concentration[a)]	Cytotoxicity[a)]	Results	References
		L5178Y mouse lymphoma cells	50–10 000 µM	5000 µM and above	5000 µM and above	+	Soriano et al. 2007
	dimethylarsinous acid	L5178Y mouse lymphoma cells	0.65–1.51 µM	1.51 µM	–	+	Kligerman et al. 2003
	dimethylarsinic acid	L5178Y mouse lymphoma cells	100–10 000 µM	10 000 µM and above	10 000 µM and above	+	Soriano et al. 2007
		L5178Y mouse lymphoma cells	2000–10 000 µg/ml	–	6000 µg/ml and above	–	Moore et al. 1997
gpt$^{+/-}$	methylarsonous acid	GT cells	0.6–1.0 µM	0.6 µM and above	0.51 µM and above	+	Klein et al. 2007
	dimethylarsinous acid	GT cells	0.3–0.4 µM	–	0.15 µM and above	–	Klein et al. 2007

[a)] simultaneous induction of bi-nuclear or multi-nuclear cell nuclei (evidence of spindle disturbances), (+) = weakly positive;
SCE = sister chromatid exchange; CA = test for structural chromosomal aberrations; SCGE assay = alkaline single cell gel electrophoresis assay;
SS breaks = single strand breaks

The incubation for 6 hours of V79 cells in 1 mM **dimethylarsinic acid** with Escherichia coli A3-6 but without cysteine produced a questionably significant increase in chromosomal aberrations, whereas the incidences of C-mitosis, tetraploidy, mitotic arrest and sister chromatid exchange were not significantly increased. In this system, **trimethylarsine oxide** was not found to be genotoxic either with or without the addition of cysteine (Kuroda et al. 2004). An unidentified metabolite of dimethylarsinic acid formed in the presence of Escherichia coli induced a significant increase in C-mitosis, mitotic arrest, tetraploidy, chromosomal aberrations and sister chromatid exchange (Kuroda et al. 2004). This metabolite is quite probably dimethylthioarsinic acid (Leffers et al. 2013 a). 10 µM **dimethylthioarsinic acid** was demonstrated to cause effective mitotic arrest (Naranmandura et al. 2007 a).

The results of the studies of the genotoxicity of methylarsenic compounds in vitro are shown in Table 8.

Summary:

Methylarsenic compounds are not mutagenic in bacteria, but are clastogenic and aneugenic and impair DNA repair in vitro in mammalian cells.

5.6.2 In vivo

Somatic cells

The results of genotoxicity studies in rats and mice are shown in Table 9.

In CD1 mice, the intraperitoneal injection of **dimethylarsinic acid** doses of 300 mg/kg body weight caused aneuploid bone marrow cells (Kashiwada et al. 1998). After oral administration of 1500 mg/kg body weight, DNA strand breaks were found only after 12 hours in lung cells, but not in liver or kidney cells. After 24 hours, DNA damage could no longer be demonstrated (Yamanaka et al. 1989; Yamanaka and Okada 1994).

After the administration of **dimethylarsinic acid** doses of 7.5 mg/kg body weight and day with the drinking water for 6 weeks, the formation of 8-hydroxydeoxyguanosine was detected in the liver (Wanibuchi et al. 1997). After single oral doses of **dimethylarsinic acid** of 720 mg/kg body weight, also oxidative DNA damage was found in the lungs and bladder (Yamanaka et al. 2003).

In Muta™ mice, intraperitoneal injection of **dimethylarsinic acid** (10.6 mg/kg body weight and day) on five consecutive days was not found to cause point mutations or micronuclei in peripheral blood reticulocytes. There were also no point mutations in lung, kidney, bladder or bone marrow cells (Noda et al. 2002).

Germ cells

The dominant lethal test described in Section 5.5.1, in which mice were given oral doses of **methylarsonic acid** of up to 119 mg/kg body weight (Prukop and Savage 1986), is not valid because the documentation was insufficient and the study was carried out inadequately (for example, the duration of treatment was too short and the number of animals used was too small), and can therefore not be used to assess the germ cell mutagenicity of methylarsenic compounds.

Table 9 Studies of the in vivo genotoxicity of methylarsenic compounds

Test system	Species	Dose [mg/kg body weight]	Results	References
8-OHdG, **liver**	**rat**, F344	about 40 mg **methylarsonic acid**/kg body weight and day, 20 days, in the drinking water	–	Kinoshita et al. 2007 b
		about 7.5 mg **dimethylarsinic acid**/kg body weight and day, 6 weeks, in the drinking water	+	Wanibuchi et al. 1997
		about 8 mg **trimethylarsine oxide**/kg body weight and day, 104 weeks, in the drinking water	+	Shen et al. 2003 b
		about 40 mg **trimethylarsine oxide**/kg body weight and day, 15 and 20 days, in the drinking water	+	Kinoshita et al. 2007 b
8-OHdG, **bladder**	**rat**, F344	about 40 mg **dimethylarsinic acid**/kg body weight and day, 20 days, in the drinking water	+	Kinoshita et al. 2007 b
		about 8 mg **dimethylarsinic acid**/kg body weight and day, 104 weeks, in the drinking water	+	Wei et al. 2002
8-OHdG, **kidneys**	**rat**, NBR	0, 5, 10 or 20 mg **dimethylarsinic acid**/kg body weight and day, 5×/week, 4 weeks, oral	+ (10 mg/kg body weight and above)	Vijayaraghavan et al. 2001
inhibition of DNA repair, bladder cells	**rat**, F344	100 mg **dimethylarsinic acid**/l drinking water (about 15 mg/kg body weight and day), 1 week, 1× cyclophosphamide	–	Wang et al. 2009 a

Table 9 (continued)

Test system	Species	Dose [mg/kg body weight]	Results	References
DNA breaks, bladder cells, (comet assay)	**rat**, F344	100 mg **dimethylarsinic acid**/l drinking water (about 15 mg/kg body weight and day), 1 week	–	Wang et al. 2009 a
DNA SS breaks, lungs, (alkaline elution)	**mouse**, CD1	1500 mg **dimethylarsinic acid**/kg body weight, oral	+ (after 12 hours) – after (24 hours)	Yamanaka and Okada 1994; Yamanaka et al. 1989
DNA SS breaks, liver, spleen, kidneys or testes, (alkaline elution)		1500 mg **dimethylarsinic acid**/kg body weight, oral	–	Yamanaka and Okada 1994
aneuploidy, bone marrow		300 mg **dimethylarsinic acid**/kg body weight, i. p.	+ (after 24 hours)	Kashiwada et al. 1998
point mutations, peripheral reticulocytes	**mouse**, Muta™	10.6 mg **dimethylarsinic acid**/kg body weight, i. p.	–	Noda et al. 2002
point mutations, lungs, kidneys, bladder or bone marrow			–	
micronuclei, peripheral reticulocytes			–	
micronuclei, bone marrow	**rat**, F344	100 mg **dimethylarsinic acid**/l drinking water (about 15 mg/kg body weight and day), 1 week	–	Wang et al. 2009 a

8-OHdG = 8-hydroxydeoxyguanosine, DNA SS breaks = DNA single strand breaks, i. p. = intraperitoneal

Summary:

Methylarsenic compounds cause oxidative DNA damage in the liver and kidney cells of rats and DNA strand breaks in the lungs and aneuploidy in bone marrow cells of mice. Methylarsenic compounds do not induce point mutations in lung, kidney, bladder or bone marrow cells of Muta™ mice. In animal experiments, methylarsenic compounds were found to be clastogenic and aneugenic.

There are no studies available of the germ cell mutagenicity of methylarsenic compounds which fulfil present-day requirements.

5.7 Carcinogenicity

5.7.1 Short-term studies

A study available only in summary form reports that dermal application of **dimethylarsinous acid** (no other details) increases the 8-oxo-7,8-dihydroguanine concentration in the epidermis and leads to the formation of skin tumours (no other details) (An et al. 2009).

Six-week-old A/J and ddY mice were given intraperitoneal injections of 0 or 5.3 mg **dimethylarsinic acid**/kg body weight and day or 6.0 mg **trimethylarsine**/kg body weight and day for 5 days. After a 25-week recovery period, the lungs, liver, kidneys, spleen, stomach and bladder were examined microscopically for tumours. A significantly increased tumour incidence was found only in the lungs in both strains and only after dimethylarsinic acid doses but not, however, after the injections with trimethylarsine (Yamanaka et al. 2009).

The administration of 0, 10, 50, 100 or 150 mg **methylarsonous acid**/l drinking water (methylarsonous acid doses of about 0, 1.25, 6.25, 12.5 or 18.75 mg/kg body weight and day) for 26 weeks did not increase the incidence of skin tumours in transgenic K6/OCD mice (Chen et al. 2008).

In rats exposed to **dimethylarsinic acid** via the drinking water, a significant increase in proliferating cells in the surface epithelium of the bladder was found after doses of 0.75 mg/kg body weight and day and above for 32 weeks (Wanibuchi et al. 1996). After 22 weeks of treatment no preneoplastic changes or tumours occurred at **dimethylarsinic acid** doses up to 30 mg/kg body weight and day (Yamamoto et al. 1995, 1997).

A/J mice were given **dimethylarsinic acid** doses of up to about 50 mg/kg body weight and day for 25 weeks, or doses of up to about 28 mg/kg body weight and day for 50 weeks with the drinking water (see Table 10). The number of lung tumours per animal and of hyperplasia in the lungs was significantly increased only after the longer treatment period of 50 weeks at doses of 3.5 mg dimethylarsinic acid/kg body weight and day and above. After dimethylarsinic acid doses of 28 mg/kg body weight and day there was a significantly increased number of alveolar and papillary adenomas. Apart from the lungs, no other organs were examined (Hayashi et al. 1998). In $Ogg^{-/-}$ mice, which are incapable of repairing oxidative DNA damage, **dimethylarsinic acid** doses of about 8 mg/kg body weight and day for 72 weeks (see Table 10) induced significantly increased incidences of adenomas and adenocarcinomas in the lungs, and also of lymphomas and leukaemia (Kinoshita et al. 2007 a).

Table 10 Short-term studies of the carcinogenicity of dimethylarsinic acid in mice

Author:	Hayashi et al. 1998			
Substance:	**dimethylarsinic acid** (purity 99%)			
Species:	**mice**, A/J, 10–14 ♂ per group			
Administration route:	0, 50, 200 or 400 mg dimethylarsinic acid/l drinking water			
Dose:	25 weeks: about 0, 6.25, 25 or 50 mg dimethylarsinic acid/kg body weight and day; 50 weeks: about 0, 3.5, 14 or 28 mg dimethylarsinic acid/kg body weight and day			
Duration:	25 or 50 weeks			
Toxicity:	–			
	Dimethylarsinic acid [mg/l]			
	0	50	200	400
Lung tumours after 25 weeks				
incidence	2/10 (20%)	3/10 (30%)	4/10 (40%)	3/10 (30%)
tumours/animal	0.20 ± 0.42	0.30 ± 0.48	0.50 ± 0.71	0.40 ± 0.70
alveolar or papillary adenomas	2/10 (20%)	3/10 (30%)	3/10 (30%)	3/30 (30%)
Lung tumours after 50 weeks				
incidence	7/14 (50%)	10/14 (71%)	9/14 (64%)	11/14 (79%)
tumours/animal	0.50 ± 0.52	1.07 ± 1.00*	1.07 ± 1.07*	1.36 ± 1.01*
hyperplasia	0/14 (0%)	6/14 (43%)**	3/14 (21%)	4/14 (29%)*
alveolar or papillary adenomas	2/14 (14%)	5/14 (36%)	7/14 (50%)*	10/14 (71%)**
adenocarcinomas	1/14 (7%)	3/14 (21%)	4/14 (29%)	3/14 (21%)
no other organs were examined				
Author:	Kinoshita et al. 2007 a			
Substance:	**dimethylarsinic acid** (purity 99%)			
Species:	**mice**, $Ogg^{-/-}$ and $Ogg^{+/+}$(C57Bl/6 J), 5–6 ♂ and 5–6 ♀ each			
Administration route:	0 or 200 mg dimethylarsinic acid/l drinking water			
Dose:	about 14 mg dimethylarsinic acid/kg body weight and day			
Duration:	72 weeks			
Toxicity:	**$Ogg^{-/-}$ mice**: about 14 mg dimethylarsinic acid/kg: relative weights of the lungs, liver, spleen ↑, induction of cell proliferation, signal transduction and genes responsible for xenobiotic metabolism, lungs: increased formation of microvilli with number of mitochondria ↑			

Table 10 (continued)

	Ogg$^{-/-}$ mice	
	Dimethylarsinic acid [mg/kg body weight and day]	
	0	about 14
lymphomas or leukaemia	0/10 (0%)	4/10 (40%)[1)]
Liver		
carcinomas	0/10 (0%)	1/10 (10%)
Lung		
adenomas	0/10 (0%)	2/10 (20%)
adenocarcinomas	0/10 (30%)	3/10 (30%)
adenomas and adenocarcinomas	0/10 (0%)	5/10 (50%)*
Mammary gland		
adenocarcinomas	0/10 (0%)	1/10 (10%)

no increased tumour incidences were found in **Ogg$^{+/+}$ mice** after the administration of dimethylarsinic acid, although adenocarcinomas were found in the kidneys (1/12) and mammary gland (1/12) in addition to one sarcoma of the skin (1/12);
no other organs were examined
no separate data given for ♂ and ♀ animals

[1)] $p = 0.05$; $^{*}p \leq 0.05$; $^{**}p \leq 0.01$

Summary:

In short-term studies with rats, dimethylarsinic acid did not cause an increase in tumour incidences in the investigated organs, such as the bladder and lungs, after 32 weeks of treatment. In male mice, a significant increase in the incidence of alveolar and papillary adenomas in the lungs was found after 50 weeks of treatment with dimethylarsinic acid doses of 3.5 mg/kg body weight and day and above. This indicates that methylated arsenic compounds have an initiating effect.

Initiation–promotion studies

In various initiation–promotion studies in male rats, the effects of methylated arsenic compounds on preneoplastic changes or tumours in the lungs, kidneys, bladder, liver and also in the oesophagus, forestomach, intestine and thymus were investigated. These studies are shown in Table 11.

In male F344 rats, a study with intraperitoneal injection of the initiators diethylnitrosamine (DEN), N-methyl-N-nitrosourea (MNU) and 1,2-dimethylhydrazine (DMH) within 4 weeks, with additional treatment with N-butyl-N-(4-hydroxybutyl)-nitrosamine (BBN) and N-bis(2-hydroxypropyl)nitrosamine (DHPN) in the drinking water resulted in significantly increased tumour incidences in the bladder,

liver and kidneys following a 6-month promotion phase with **dimethylarsinic acid**. The incidences of hyperplasia, papillomas and carcinomas of the bladder were significantly increased after dimethylarsinic acid doses of 3.75 mg/kg body weight and day and above. At dose levels of about 15 mg/kg body weight and day and above, the incidences of adenomas and renal cell tumours of the kidneys and hyperplasia, nodules and hepatocellular carcinomas of the liver were significantly increased.

In the oesophagus, forestomach, intestine and thymus, no preneoplasms or tumours developed (Yamamoto et al. 1995, 1997).

Bladder

In the bladder of NBR rats treated with 0.05% BBN in the drinking water for 4 weeks and subsequently with **dimethylarsinic acid** doses of about 12.5 mg/kg body weight and day in the drinking water for 32 weeks, a significant increase in simple, papillary or nodular hyperplasia was found, but no significantly increased incidence of carcinomas (Li et al. 1998). In F344 rats investigated using the same study design, a dose-dependent increase in the incidence of papillomas and carcinomas in the bladder was observed even after doses of as little as 1.88 mg **dimethylarsinic acid**/kg body weight and day (Wanibuchi et al. 1996).

Liver

After initiation with 30 mg diethylnitrosamine/kg body weight and partial hepatectomy, the incidence of basophilic foci in the liver was significantly increased in Wistar rats given **dimethylarsinic acid** doses of 3.8 mg/kg body weight and day with the drinking water for 6 months (Johansen et al. 1984). After pretreatment with 200 mg diethylnitrosamine/kg body weight and after partial hepatectomy, subsequent promotion with **dimethylarsinic acid** for 2 weeks led in F344 rats to significantly increased activities of ornithine decarboxylase (ODC) and spermidine/spermine N-acetyltransferase (SAT, limiting enzyme of polyamine biosynthesis) in the liver at dimethylarsinic acid doses of 0.75 mg/kg body weight and day and above. The increase in ODC activity is regarded as a marker for cell proliferation, and that of SAT is associated with carcinogenesis in the skin, bladder and liver. In addition, at dose levels of 1.88 mg dimethylarsinic acid/kg body weight and day and above, the number and size of foci containing the placental form of glutathione S-transferase (GST-P) were increased (Wanibuchi et al. 1997). In a comparative investigation, after initiation with 200 mg diethylnitrosamine/kg body weight and subsequent partial hepatectomy, F344 rats were given 0 or 7.5 mg **methylarsonic acid**, **dimethylarsinic acid** or **trimethylarsine oxide** per kg body weight and day for 6 weeks in the drinking water. In the liver, increased GST-P positive foci, 8-hydroxydeoxyguanosine and CYP2B1 protein were formed by the three methylated arsenic compounds (Nishikawa et al. 2002). In male F344/DuCrj rats, after initiation with 100 mg DEN/kg body weight, 80 mg MNU/kg body weight, 160 mg DMH/kg body weight, 0.5% BBN in the drinking water (weeks 1 and 2), 0.1% DHPN in the drinking water (weeks 3 and 4) and promotion with **dimethylarsinic acid** (from weeks 8 to 30), the frequency of early stages of carcinogenesis, such as changed foci and hyperplastic nodules was significantly increased, and the incidence of hepatocellular carcinomas was also significantly increased at dose levels of about 15 mg dimethylarsinic acid/kg body weight and day and above (Yamamoto et al. 1995, 1997).

Kidneys

Initiation with 100 mg DEN/kg body weight, 80 mg MNU/kg body weight, 160 mg DMH/kg body weight, 0.5% BBN in the drinking water, 0.1% DHPN in the drinking water and promotion with **dimethylarsinic acid** significantly increased the incidence of adenomas and renal cell carcinomas in male F344/DuCrj rats at dose levels of about 15 mg dimethylarsinic acid/kg body weight and day and above (Yamamoto et al. 1995, 1997).

When the foetuses of mice were exposed to sodium arsenite and later the male offspring were given **dimethylarsinic acid** in the drinking water (14 mg/kg body weight and day) for a further 104 weeks, considerably higher tumour incidences were found than with dimethylarsinic acid alone or even with arsenite alone (Tokar et al. 2012).

No substance-related significantly increased tumour incidences were found in the nasal cavity, lungs, oesophagus, forestomach, intestine, thymus or skin of male F344/DuCrj rats after initiation with DEN, MNU, DMH, BBN or DHPN and promotion with **dimethylarsinic acid** doses in the drinking water of up to about 30 mg/kg body weight (Yamamoto et al. 1997).

Table 11 Initiation–promotion studies with methylarsenic compounds

Author:	Yamamoto et al. 1995
Substance:	**dimethylarsinic acid** (purity 99%)
Species:	**rat**, F344/DuCrj, 12–20 ♂ per group
Treatment:	**multiorgan test**, **I. with pretreatment** initiation: 100 mg **DEN**/kg body weight (1 × i.p.), + 4 × 20 mg **MNU**/kg body weight (i.p.; on days 5, 8, 11 and 14), + 4 × 40 mg **DMH**/kg body weight (s.c.; on days 18, 22, 26 and 30), **simultaneously:** **+ 0.5% BBN** in the drinking water (weeks 1 and 2), **+ 0.1% DHPN** in the drinking water (weeks 3 and 4), 2 weeks recovery, + 0, 50, 100, 200 or 400 mg **dimethylarsinic acid**/l drinking water (doses of about 0, 3.75, 7.5, 15 or 30 mg dimethylarsinic acid/kg body weight and day) (weeks 8–30); **II. without pretreatment** + 0, 100 or 400 mg **dimethylarsinic acid**/l drinking water (doses of about 0, 7.5 or 15 mg dimethylarsinic acid/kg body weight and day) (weeks 8–30)
Dose:	pretreatment + about 0, 3.75, 7.5, 15 or 30 mg **dimethylarsinic acid**/kg body weight and day
Duration:	32 weeks
Toxicity:	no data

Table 11 (continued)

	Pretreatment + dimethylarsinic acid [mg/kg body weight and day]				
	0	about 3.75	about 7.5	about 15	about 30
Tumours and preneoplasms					
Bladder					
hyperplasia	4/20 (20%)	13/20 (65%)**	14/19 (74%)***	11/20 (55%)*	11/20 (55%)*
papillomas	1/20 (5%)	12/20 (60%)***	12/19 (63%)***	11/20 (55%)***	7/20 (35%)***
carcinomas	1/20 (5%)	10/20 (50%)**	11/19 (58%)***	12/20 (60%)***	13/20 (65%)***
animals with tumours	2/20 (10%)	17/20 (85%)***	16/19 (84%)***	17/20 (85%)***	16/20 (80%)***
Kidney					
adenomas	1/20 (5%)	3/20 (15%)	1/19 (5%)	7/20 (35%)*	3/20 (15%)
adenocarcinomas	0/20 (0%)	0/20 (0%)	2/19 (11%)	1/20 (5%)	7/20 (35%)*
renal cell tumours	1/20 (5%)	3/20 (15%)	2/19 (11%)	8/20 (40%)**	9/20 (45%)*
nephroblastomas	4/20 (20%)	0/20 (0%)	4/19 (12%)	6/20 (30%)	9/20 (45%)
animals with tumours	5/20 (25%)	3/20 (15%)	6/19 (32%)	13/20 (65%)*	13/20 (65%)*
Liver					
changed foci	10/20 (50%)	12/20 (60%)	14/19 (74%)	19/20 (95%)**	20/20 (100%)***
hyperplastic nodules	0/20 (0%)	0/20 (0%)	2/19 (11%)	9/20 (45%)***	7/20 (35%)**
hepatocellular carcinomas	0/20 (0%)	2/20 (10%)	0/20 (0%)	8/20 (40%)**	8/20 (40%)**
animals with tumours	0/20 (0%)	2/20 (10%)	2/19 (11%)	17/20 (85%)***	13/20 (65%)***

without pretreatment + dimethylarsinic acid, incidence of preneoplastic changes or tumours not increased

Table 11 (continued)

Author:	Yamamoto et al. 1997
Substance:	**dimethylarsinic acid** (purity 99%)
Species:	**rat**, F344/DuCrj, 12–20 ♂ each
Treatment:	**multiorgan test**, **I. with pretreatment** initiation: 100 mg **DEN**/kg body weight (1 × i. p.) + 4 × 20 mg **MNU**/kg body weight (i. p.; on days 5, 8, 11 and 14); + 4 × 40 mg **DMH**/kg body weight (s. c.; on days 18, 22, 26 and 30); **simultaneously:** **+ 0.5% BBN** in the drinking water (weeks 1 and 2); **+ 0.1% DHPN** in the drinking water (weeks 3 and 4); 2 weeks recovery; + 0, 50, 100, 200 or 400 mg **dimethylarsinic acid**/l drinking water (doses of about 0, 3.75, 7.5, 15 or 30 mg dimethylarsinic acid/kg body weight and day) (weeks 8–30) **II. without pretreatment** 0, 100 or 400 mg **dimethylarsinic acid**/l drinking water (doses of about 0, 7.5 or 15 mg dimethylarsinic acid/kg body weight and day) (weeks 8–30)
Dose:	pretreatment + about 0, 3.75, 7.5, 15 or 30 mg **dimethylarsinic acid**/kg body weight and day
Duration:	32 weeks
Toxicity:	–

	Pretreatment + dimethylarsinic acid [mg/kg body weight and day]				
	0	about 3.75	about 7.5	about 15	about 30
Tumours					
Thyroid gland					
tumours	3/20 (15%)	2/20 (10%)	8/20 (42%)	6/20 (30%)	9/20 (45%)*

dimethylarsinic acid with pretreatment:
no substance-related significantly increased tumour incidences in nasal cavity, lungs, oesophagus, forestomach, intestines, thymus or skin

dimethylarsinic acid without pretreatment:
bladder: increased incidence of simple hyperplasia, incidence of preneoplastic changes or tumours not increased

Author:	Li et al. 1998
Substance:	**dimethylarsinic acid** (purity 99%)
Species:	**rat**, NBR, 8 ♂ each
Treatment:	initiation: 0.5% BBN in the drinking water (4 weeks); promotion: 0 or 100 mg **dimethylarsinic acid**/l drinking water (doses of about 0 or 12.5 mg dimethylarsinic acid/kg body weight and day) (weeks 5–32); examination after 36 weeks
Dose:	BBN + about 0 or 12.5 mg **dimethylarsinic acid**/kg body weight and day

Table 11 (continued)

Duration:	36 weeks				
Toxicity:	–				
	BBN + dimethylarsinic acid [mg/kg body weight and day]				
	0		12.5		
Tumours and preneoplasms of the bladder					
simple hyperplasia	3/ 8 (38%)		8/ 8 (100%)*		
papillary or nodular hyperplasia	0/ 8 (0%)		6/ 8 (75%)**		
papillary carcinomas	0/ 8 (0%)		3/ 8 (38%)		
animals with tumours	0/20 (0%)		2/20 (10%)		
Author:	Wanibuchi et al. 1996				
Substance:	**dimethylarsinic acid** (purity 99%)				
Species:	**rat**, F344, 20 ♂ each				
Treatment:	initiation: 0.05% BBN in the drinking water (4 weeks); promotion: 0, 2, 10, 25, 50 or 100 mg **dimethylarsinic acid**/l drinking water (doses of about 0, 0.15, 0.75, 1.88, 3.75 or 7.5 mg dimethylarsinic acid/kg body weight and day) (32 weeks); examination after 34 weeks				
Dose:	BNN + about 0, 0.15, 0.75, 1.88, 3.75 or 7.5 mg **dimethylarsinic acid**/kg body weight and day				
Duration:	8 weeks				
Toxicity:	mortality: BBN + 1.88 mg dimethylarsinic acid/kg body weight and day (1/20); without initiation + 7.5 mg dimethylarsinic acid/kg body weight and day (1/12)				
	BBN + dimethylarsinic acid [mg/kg body weight and day]				
	0	0.75	1.88	3.75	7.5
Tumours and preneoplasms					
Bladder					
papillary or nodular hyperplasia	14/20 (70%)	14/20 (70%)	18/20 (95%)	20/20 (100%)*	20/20 (100%)*
papillomas	3/20 (15%)	7/20 (35%)	11/19 (58%)**	13/20 (65%)**	17/20 (85%)***
carcinomas	1/20 (5%)	3/20 (15%)	7/20 (35%)*	10/20 (50%)**	12/20 (60%)***
pretreatment with BBN and dimethylarsinic acid doses of about 0.15 mg/kg body weight and day: incidence of hyperplasia, papillomas or carcinomas not increased; without pretreatment with BBN: significant increase in the proliferation of cells of the surface epithelium of the bladder, incidences of hyperplasia, papillomas or carcinomas not increased; no other organs examined					

Table 11 (continued)

Author:	Wanibuchi et al. 1997			
Substance:	**dimethylarsinic acid** (purity 99%)			
Species:	**rat**, F344, 10 ♂ each			
Treatment:	initiation: 200 mg DEN/kg body weight (i. p.); 2 weeks recovery; partial hepatectomy (PH); promotion: 0, 25, 50 or 100 mg **dimethylarsinic acid**/l drinking water (doses of about 0, 1.88, 3.75 or 7.5 mg dimethylarsinic acid/kg body weight and day) (6 weeks); without initiation, without PH + 100 mg dimethylarsinic acid/l drinking water (doses of about 7.5 mg dimethylarsinic acid/kg body weight and day) (6 weeks) examination after 8 weeks			
Dose:	DEN + PH + about 0, 1.88, 3.75 or 7.5 mg **dimethylarsinic acid**/kg body weight and day			
Duration:	8 weeks			
Mortality:	DEN + PH + 3.75 (6/10) + 7.5 mg dimethylarsinic acid/kg body weight (5/10)			
	DEN + PH + dimethylarsinic acid [mg/kg body weight]			
	0	1.88	3.75	7.5
Preneoplasms				
Liver				
number and size of GST-P positive foci	–	↑*	↑**	↑**
Author:	Nishikawa et al. 2002			
Substance:	**methylarsonic acid** (purity 99.9%), **dimethylarsinic acid** (purity 99%) or **trimethylarsine oxide** (purity 99.9%)			
Species:	**rat**, F344, 20 ♂ each			
Treatment:	initiation: 200 mg DEN/kg body weight (i. p.); 2 weeks recovery; partial hepatectomy; promotion: 100 mg **methylarsonic acid**, **dimethylarsinic acid** or **trimethylarsine oxide**/l drinking water (6 weeks)			
Dose:	DEN + about 0 or 7.5 mg **methylarsenic compound**/kg body weight and day			
Duration:	8 weeks			
Toxicity:	methylarsonic acid and dimethylarsinic acid: body weights ↓, dimethylarsinic acid: drinking water consumption ↑			

Table 11 (continued)

	DEN + PH + methylarsenic compound [mg/kg body weight]		
	0	about 7.5	
Liver			
number and size of GST-P positive foci	methylarsonic acid	–	↑*
	dimethylarsinic acid	–	↑*
	trimethylarsine oxide	–	↑*
8-OHdG formation	methylarsonic acid	–	↑*
	dimethylarsinic acid	–	↑*
	trimethylarsine oxide	–	↑*
CYP2B1 level	methylarsonic acid	–	↑*
	dimethylarsinic acid	–	↑ not significant
	trimethylarsine oxide	–	↑ not significant

Author:	Johansen et al. 1984
Substance:	**dimethylarsinic acid** (purity not specified)
Species:	**rat**, Wistar, 7–11 ♂ each
Treatment:	partial hepatectomy; initiation: 30 mg DEN/kg body weight (i. p.); 7 days recovery; promotion: 80 mg dimethylarsinic acid/l drinking water (6 months)
Dose:	DEN + 0 or 3.8 ± 0.5 mg **dimethylarsinic acid**/kg body weight and day
Duration:	6 or 10 months
Toxicity:	no data

After treatment with dimethylarsinic acid for 6 months:

	DEN + PH + dimethylarsinic acid [mg/l]	
	0	80
Kidney		
adenomas or carcinomas	2/11 (29%)	3/7 (42%)
Liver		
foci (mean number)		
eosinophilic	0.79 ± 0.32	1.38 ± 0.49
basophilic	0.82 ± 0.33	2.29 ± 0.68*
nodules		
neoplastic	–	0.14 ± 0.14

After treatment with dimethylarsinic acid for 10 months:

	DEN + PH + dimethylarsinic acid [mg/l]	
	0	80
Liver		
carcinomas	no data	2/13 (15%)

Table 11 (continued)

without pretreatment + dimethylarsinic acid: incidence of preneoplastic changes or tumours not increased			
Author:	Tokar et al. 2012		
Substance:	**dimethylarsinic acid** (purity 98%)		
Species:	**mouse**, CD1, 50 ♂ control animals, 23 ♂ treated animals		
Treatment:	dams: 0 or 25 mg sodium arsenite/l drinking water promotion: 0 or 200 mg **dimethylarsinic acid**/l drinking water		
Dose:	about 0 or 14 mg **dimethylarsinic acid**/kg body weight and day		
Duration:	dams: GD 8–18 ♂ offspring after weaning: 104 weeks		
Toxicity:	–		
	Arsenite + dimethylarsinic acid [mg/kg body weight and day]		
	0	14	
Survivors	no difference between untreated and treated animals		
Tumours and preneoplasms			
Lung			
adenocarcinomas	♂	3/49 (6%)	8/23 (35%)*
Liver			
carcinomas	♂	3/49 (6%)	10/23 (43%)*
Bladder			
hyperplasia	♂	1/49 (2%)	8/23 (35%)*
Kidney			
hyperplasia	♂	0/49 (0%)	4/23 (17%)*
carcinomas	♂	0/49 (0%)	3/23 (13%)*
Adrenal gland (cortex)			
adenomas	♂	0/49 (0%)	11/23 (48%)*

*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$

BBN: N-butyl-N-(4-hydroxybutyl)-nitrosamine, DEN: diethylnitrosamine, DHPN: N-bis(2-hydroxypropyl)nitrosamine, DMH: 1,2-dimethylhydrazine, MNU: N-methyl-N-nitrosourea, PH = partial hepatectomy

Summary:

In various initiation–promotion studies with male rats and mice, the investigated methylated arsenic compounds caused preneoplastic changes or tumours in the bladder, liver, kidneys or lungs but not in the oesophagus, forestomach, intestines and thymus. Therefore, the methylated arsenic compounds are considered to be tumour promotors.

5.7.2 Long-term studies

Carcinogenicity studies (see Table 12) revealed that **methylarsonic acid** administered to rats with the drinking water caused a significantly increased incidence of simple hyperplasia in the bladder at methylarsonic acid doses of 2 mg/kg body weight and day and above. In the liver, the numbers and size of glutathione S-transferase placental form positive foci were significantly increased at methylarsonic acid doses of 8 mg/kg body weight and day (Shen et al. 2003 a). In rats, **dimethylarsinic acid** administered with the diet or the drinking water led to a significant increase in the incidence of simple (dimethylarsinic acid doses of 2 mg/kg body weight and above) or papillary and nodular hyperplasia (doses of 5 mg/kg body weight and above) (Arnold et al. 2006), papillomas (doses of 10 mg/kg body weight and above) (Wei et al. 1999) and carcinomas (doses of 5 mg/kg body weight and above) in the bladder (Arnold et al. 2006; Wei et al. 1999). In the liver of rats, **trimethylarsine oxide** (doses of 8 mg/kg body weight) administered with the drinking water caused a significant increase in hepatocellular adenomas (Shen et al. 2003 b).

Table 12 Studies of the carcinogenicity of methylarsenic compounds in rats

Author:		Shen et al. 2003 a		
Substance:		**methylarsonic acid** (purity 98.9%–100%)		
Species:		**rat**, F344/N, 60 ♂ and 60 ♀ each		
Administration route:		0, 50 or 200 mg methylarsonic acid/l drinking water		
Dose:		about 0, 2 or 8 mg **methylarsonic acid**/kg body weight and day		
Duration:		104 weeks		
Toxicity:		–		
		Dose [mg methylarsonic acid/kg body weight and day]		
		0	2	8
Survivors		no difference between untreated and treated animals		
Preneoplasms				
Bladder				
hyperplasia				
simple	♂	4/42 (10%)	18/42 (43%)***	19/45 (42%)***
Liver				
GST-P foci	♂			
number/cm²	♂	12.6	16.6	22.9*
size [mm²/cm²]	♂	0.4	0.9	1.9*
no other significant differences in the tumour incidences between treated and untreated animals				

Table 12 (continued)

Author:	Wei et al. 1999, 2002			
Substance:	**dimethylarsinic acid** (purity 99%)			
Species:	**rat**, F344, 36 ♂ each			
Administration route:	0, 12.5, 50 or 200 mg dimethylarsinic acid/l drinking water			
Dose:	about 0, 0.6, 2.5 or 10 mg **dimethylarsinic acid**/kg body weight			
Duration:	104 weeks			
Toxicity:	**2.5 mg/kg body weight and above**: drinking water intake ↑			
	Dimethylarsinic acid [mg/kg body weight and day]			
	0	0.6	2.5	10
Survivors				
97 weeks	28/36 (78%)	33/36 (92%)	31/36 (86%)	31/36 (86%)
104 weeks	25/36 (69%)	28/36 (78%)	28/36 (78%)	24/36 (67%)
Tumours and preneoplasms				
Bladder				
hyperplasia	0/28 (0%)	0/33 (0%)	(12/31) (39%)***	(14/31) (45%)***
papillomas	0/28 (0%)	0/33 (0%)	(2/31) (6%)	(2/31) (6%)
carcinomas	0/28 (0%)	0/33 (0%)	(6/31) (19%)*	(12/31) (39%)***
no other organs examined				

Author:	Arnold et al. 2006; Cohen et al. 2007				
Substance:	**dimethylarsinic acid** (purity 98.9%–100%)				
Species:	**rat**, F344/N, 60 ♂ and 60 ♀ each				
Administration route:	0, 2, 10, 40 or 100 mg dimethylarsinic acid/kg diet				
Dose:	about 0, 0.1, 0.5, 2 or 5 mg dimethylarsinic acid/kg body weight and day				
Duration:	104 weeks				
Toxicity:	**about 0.1 mg/kg body weight and above**: drinking water intake ↑, (♀): relative adrenal weights ↑; **about 2 mg/kg body weight and above**: bladder: submucosal lymphocytic infiltration (♂) and urothelial vacuolar degeneration (♀); kidney: calcinosis (medulla); **about 5 mg/kg body weight and above**: kidney: tubular cystic dilation (medulla), necrosis (papilla); thyroid: size of follicular cells ↑				
	Dimethylarsinic acid [mg/kg body weight and day]				
	0	0.1	0.5	2	5
Survivors	no difference between untreated and treated animals				

Table 12 (continued)

Tumours and preneoplasms							
Bladder							
hyperplasia							
simple	♂	0/60 (0%)	0/59 (0%)	0/60 (0%)	4/58	(7%)	35/59 (59%)***
	♀	0/60 (0%)	0/59 (0%)	0/60 (0%)	28/59	(47%)***	40/60 (67%)***
papillary/nodular	♂	0/60 (0%)	0/59 (0%)	0/60 (0%)	2/58	(3%)	5/59 (8%)*
	♀	0/60 (0%)	1/59 (2%)	0/60 (0%)	1/59	(2%)	8/60 (13%)**
papillomas	♂	0/60 (0%)	0/59 (0%)	1/60 (2%)	1/58	(2%)	0/59 (0%)
	♀	0/60 (0%)	0/59 (0%)	0/60 (0%)	0/59	(0%)	4/60 (7%)
carcinomas	♂	0/60 (0%)	1/59 (2%)	0/60 (0%)	0/58	(0%)	2/59 (3%)
	♀	0/60 (0%)	0/59 (0%)	0/60 (0%)	0/59	(0%)	6/60 (10%)*
papillomas and carcinomas	♂	0/60 (0%)	1/59 (2%)	0/60 (0%)	1/58	(2%)	2/59 (3%)
	♀	0/60 (0%)	0/59 (0%)	0/60 (0%)	0/59	(0%)	10/60 (17%)

Author:	Shen et al. 2003 b			
Substance:	**trimethylarsine oxide** (purity 98.9%–100%)			
Species:	**rat**, F344/N, 42–45 ♂ each			
Administration route:	0, 50 or 200 mg trimethylarsine oxide/l drinking water			
Dose:	about 0, 2 or 8 mg **trimethylarsine oxide**/kg body weight and day			
Duration:	104 weeks			
Toxicity:	–			
		Trimethylarsine oxide [mg/kg body weight and day]		
		0	2	8
Survivors		no difference between untreated and treated animals		
Tumours				
Liver				
hepatocellular adenomas	♂	6/42 (9%)	10/42 (14%)	16/45 (24%)*
no other significant differences in tumour incidences between treated and untreated animals				

*p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001; GST-P = placental form of glutathione S-transferase

Mice seem to be less sensitive to organic arsenic compounds than rats (see Table 13). When administered with the diet, **dimethylarsinic acid** significantly increased the incidence of fibrosarcomas in female mice given dimethylarsinic acid doses of 62.5 mg/kg body weight and day (Arnold et al. 2006).

Table 13 Studies of the carcinogenicity of methylarsenic compounds in mice

Author:	Salim et al. 2003				
Substance:	**dimethylarsinic acid** (purity 100%)				
Species:	**mice**, C57/6J wild-type or $p53^{+/-}$ knockout, 30 ♂ each				
Administration route:	0, 50 or 200 mg dimethylarsinic acid/l drinking water				
Dose:	0, 3.5 or 14 mg **dimethylarsinic acid**/kg body weight and day				
Duration:	18 months				
Toxicity:	–				
	Dimethylarsinic acid [mg/kg body weight and day]				
C57/6J wild-type	0		3.5		14
malignant lymphomas	3/30 (10%)		9/30 (30%)[a)]		9/30 (30%)[a)]
induction of malignant lymphomas in treated C57/6J wild-type and $p53^{+/-}$ knockout mice, incidence significantly increased only in the middle period of the study, at the end of the study the incidence was increased (p = 0.05) only in wild-type mice					

Author:	Arnold et al. 2006					
Substance:	**dimethylarsinic acid** (purity 98.9%–100%)					
Species:	**mice**, B6C3F1, 60 ♂ and 60 ♀ each					
Administration route:	0, 8, 40, 200 or 500 mg dimethylarsinic acid/kg diet					
Dose:	about 0, 1, 5, 25 or 62.5 mg **dimethylarsinic acid**/kg body weight and day					
Duration:	104 weeks					
Toxicity:	–					
		Dimethylarsinic acid [mg/kg body weight and day]				
		0	about 1	about 5	about 25	about 62.5
Survivors		no difference between untreated and treated animals				
Tumours						
fibromas	♂	0/56 (0%)	0/56 (0%)	0/56 (0%)	0/56 (0%)	1/56 (2%)
	♀	0/56 (0%)	0/55 (0%)	0/56 (0%)	0/56 (0%)	0/56 (0%)
fibrosarcomas	♂	0/56 (0%)	0/56 (0%)	2/56 (4%)	4/56 (7%)	1/56 (2%)
	♀	3/56 (5%)	0/55 (0%)	1/56 (2%)	1/56 (2%)	6/56 (11%)*
fibromas and fibrosarcomas	♂	0/56 (0%)	0/56 (0%)	2/56 (4%)	4/56 (7%)	2/56 (4%)
	♀	3/56 (5%)	0/55 (0%)	1/56 (2%)	1/56 (2%)	6/56 (11%)*

Table 13 (continued)

Author:	Tokar et al. 2012		
Substance:	**dimethylarsinic acid** (purity 98%)		
Species:	**mice**, CD1, 50 ♂ control animals, 25 ♂ treated animals		
Administration route:	0 or 200 mg dimethylarsinic acid/l drinking water		
Dose:	about 0 or 14 mg **dimethylarsinic acid**/kg body weight and day		
Duration:	dams: GD 8–18 ♂ offspring after weaning: 104 weeks		
Toxicity:	–		
		Dimethylarsinic acid [mg/kg body weight and day]	
		0	14
Survivors		no difference between untreated and treated animals	
Tumours and preneoplasms			
Lung			
adenocarcinomas	♂	3/49 (6%)	6/25 (24%)*
Bladder			
hyperplasia	♂	1/49 (2%)	8/25 (32%)*
Adrenal gland (cortex)			
adenomas	♂	0/49 (0%)	6/25 (24%)*

a) $p = 0.056$; *$p \leq 0.05$; **$p \leq 0.01$

In a pesticide screening test in which groups of 18 male and 18 female (C57BL/6 × C3H/Anf) mice were given **dimethylarsinic acid** doses of 46.4 mg/kg body weight with the diet for about 18 months, no increase in tumour incidences was found (Innes et al. 1969). Because of the low number of animals, the short exposure duration and the inadequate documentation, this study cannot be used to evaluate the carcinogenicity of dimethylarsinic acid.

In a drinking water study, in which male CD1 mice were first exposed to **dimethylarsinic acid** in utero and after weaning were then given the substance with the drinking water for a further 104 weeks, doses of about 14 mg dimethylarsinic acid/kg body weight and day led to a significant increase in the incidences of adenocarcinomas in the lung, hyperplasia in the bladder and adenomas in the adrenal cortex (Tokar et al. 2012). As, however, this route of administration has no relevance for exposure at the workplace, the study cannot be used to evaluate the carcinogenicity of dimethylarsinic acid.

Summary:

After the administration of dimethylarsinic acid, clear carcinogenic effects were found in the bladder of rats, with significantly increased incidences of hyperplasia, nodules and carcinomas in the females at 5 mg/kg body weight and day. In another

study, the incidence of carcinomas in the bladder was significantly increased in males after doses of 2.5 mg/kg body weight and day and above. Trimethylarsine oxide administered with the drinking water caused a significant increase in liver adenomas in male F344 rats after doses of about 8 mg/kg body weight for two years. With methylarsonic acid only preneoplastic stages of carcinogenesis were found in the liver in the form of hyperplasia at 2 mg/kg body weight and day and above or GST-P positive foci at 8 mg/kg body weight and day.

Dimethylarsinic acid was carcinogenic also in mice. In a 2-year study with dietary administration, the incidence of fibrosarcomas (no other details) was significantly increased in female mice after dimethylarsinic acid doses of 62.5 mg/kg body weight and day.

6 Manifesto (MAK value/classification)

Methylarsenic compounds are the carcinogenic metabolites of arsenic and its inorganic compounds. Arsenic and inorganic arsenic compounds are proven human carcinogens causing tumours in the lung, bladder, kidneys and skin. Arsenite and its methylated metabolites are the active agents.

Carcinogenicity. In two animal studies, the metabolite dimethylarsinic acid was found to be clearly carcinogenic. This effect was not seen in other studies. In the only available study, trimethylarsine oxide caused liver adenomas, and with methylarsonic acid only preneoplastic stages of carcinogenesis, such as hyperplasia and preneoplastic foci were found. In the few animal studies of the carcinogenicity of inorganic arsenic compounds, most of which were not carried out in accordance with present-day requirements, carcinogenic effects were likewise not unequivocally demonstrated.

Methylated arsenic compounds—which are metabolites of inorganic arsenic compounds, which are carcinogenic in humans—are able to interfere with all important cellular processes; they produce genotoxic effects in vitro and in animal studies, impair cellular redox homoeostasis, interact for example with DNA and RNA, disturb genomic stability and via protein-protein interactions affect replication, transcription and DNA repair processes and also impair regulatory mechanisms of the cell cycle, apoptosis and signal transduction. The induction of carcinogenic mechanisms is easily comprehensible in view of these different effects. As, in addition, significantly increased incidences of kidney and bladder carcinomas have been found in rats, methylarsenic compounds are classified in Carcinogen Category 1.

Germ cell mutagenicity. Methylarsenic compounds are genotoxic in vitro and in animal studies. Methylarsenic compounds are bioavailable and reach the germ cells as demonstrated by the effects on the testes and ovaries in rats. The methylarsenic compounds are therefore classified in category 3A for germ cell mutagens.

Absorption through the skin. In studies with repeated dermal application, methylarsonic acid and dimethylarsinic acid produced weak systemic effects. Absorption through the skin from highly diluted solutions was demonstrated in vitro with human and mouse skin. The ready and very ready dermal absorption of satu-

rated solutions of methylarsonic acid and dimethylarsinic acid, respectively, is confirmed by the results obtained from model calculations. Methylarsenic compounds are genotoxic carcinogens, for which no safe systemic exposure can be estimated. For this reason it must be assumed that even small amounts absorbed percutaneously increase the carcinogenic risk. The methylarsenic compounds are therefore designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

MAK value and peak limitation. A MAK value cannot be derived on the basis of the available data. Peak limitation is therefore not applicable.

Prenatal toxicity. Dimethylarsinic acid has been demonstrated to be the most effective of the methylarsenic compounds. In rats, dimethylarsinic acid caused pre-implantation losses at 12 mg/kg body weight and day, and post-implantation losses, skeletal variations and delayed ossification at 36 mg/kg body weight and day and above. The NOAEL is 4 mg dimethylarsinic acid/kg body weight and day. As no MAK value can be derived, the substance is not classified in one of the pregnancy risk groups.

Sensitization. Apart from a well-documented case report, there are no clear findings available for the skin-sensitizing potential of methylarsenic compounds in humans. Animal studies or studies of the immunological effects on the airways are not available. The methylarsenic compounds are therefore not designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

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